THE PSYCHOLOGICAL DISTURBANCES OF THE CHILD UNDERGOING SURGERY-FROM ADMISSION TILL BEYOND DISCHARGE

MARIE T. AOUAD*

The first part of this particular issue is dedicated to the psychological disturbances of the child undergoing surgery-From admission till beyond discharge. It includes five articles addressing the following topics: “Preoperative anxiety”, “Premedication”, “Emergence agitation”, “Postoperative maladaptive behavioral changes” and “The child with behavioral disorders”.

Providing anesthesia in busy hospitals is sometimes synonymous with achieving rapid turnover times and coping with the pressure of long operating room schedules. This may be at the expense of depriving the most vulnerable age groups, namely children from an individualized approach which may result in compromised psychological well-being. This may be especially true in hospitals that are not solely dedicated to children. The mental status of children undergoing surgery is a major concern for anesthesiologists and other health care providers. Preservation of the children's psychic safety and taking into account their emotional needs are an integral part of the role of the pediatric anesthesiologist, as well as their physical security.

Preoperative anxiety is a relatively common phenomenon in children. In fact, approximately 40-60% of children experience anxiety regarding an impending surgical experience. Elevated levels of preoperative anxiety have been associated with difficulty in anesthetic induction, emergence agitation and the development of negative postoperative behavioral changes. The first review by Ahmed et al elaborates on the risk factors for preoperative anxiety, tools for quantifying children and parent’s anxiety, and non-pharmacological strategies which may play a part in decreasing preoperative anxiety. This review will also tackle the controversies surrounding parental presence during a child’s anesthesia induction and will provide the reader with a sound summary of the evidence that is accumulating in the literature regarding this issue.

Non-pharmacological strategies including parental presence are not in contradiction with the use of premedication in children. To achieve adequate anxiolysis, both modalities are often combined especially if children are very anxious and parents are calm. Among all premedicant drugs, oral midazolam is by far the most popular. Abdallah et al review the pharmacological properties of the different drugs that constitute the premedication armamentarium used in pediatric practice. The specific indications and side effects of the different drugs and routes of administration are emphasized.

Anxiety is not limited to the preoperative period, but is rather a continuum that extends through the whole perioperative period. The hostile hospital environment, anesthesia, surgery, pain and many other stressors constitute a major cause for mental distress that may lead to short or even long-term psychological distress.

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consequences. One of the earliest manifestations of mental distress in the postoperative period is the phenomenon called emergence agitation or delirium. Despite being extensively studied in the literature this phenomenon is still subject to controversies regarding its definition, tools used for its measurement, predisposing factors and preventive measures. The anesthesia literature related to this topic is thoroughly analyzed by Nasr et al in the third review of this special issue.

Following hospitalization, children may experience long term psychological disturbances such as sleep or eating disorders, separation anxiety, temper tantrums or new onset enuresis. These negative behavioral changes have been associated with traumatic anesthesia inductions by Eckenhoff more than 50 years ago. The relationship of such behaviors with the different stressors encountered during the hospital stay has been studied and some of the risk factors linked to its occurrence have been identified. The best tool to avoid the occurrence of these negative behaviors remain preventive and include a comprehensive approach that aims at minimizing psychological distress and encompasses all the time intervals of the hospital stay from admission till discharge. Risk factors and controversies related to long term behavioral changes, as well as strategies to reduce their occurrence are the subject of the fourth review by Yuki et al.

Children may exhibit behavioral disorders, which are the manifestation of normal development, or secondary to extraordinary life stresses. These can also be the consequence of disorders inherent to the child, such as attention deficit disorders, autism or any disorder that causes intellectual or learning disabilities. Awareness and understanding the special needs of this varied group of children is mandatory to tailor an individualized and humane approach throughout the hospital stay. In our last review by Yazbeck-Karam et al a comprehensive approach to the “difficult child” is presented.

The ultimate goal of in this issue special articles of the Middle East Journal of Anesthesiology is to increase the awareness of the Anesthesiologist about the visible and less visible psychological disturbances that accompany a child’s journey in the hospital. Our role is instrumental in tailoring a comprehensive approach to the child undergoing surgery that extends from the preoperative visit that precedes admission till discharge from the hospital. Tools and strategies to minimize children’s distress are abundant and range from extremely sophisticated and expensive setups to very simple and non-expensive tools that are of proven benefit. It is the duty of each Anesthesiology department to adopt a strategy with well-defined guidelines that best suits their resources, as well as to provide education to health care providers which is instrumental for the creation of a child friendly atmosphere in the hospital.
References

THE PSYCHOLOGICAL DISTURBANCES OF THE CHILD UNDERGOING SURGERY-FROM ADMISSION TILL BEYOND DISCHARGE

EDITORIAL

PULMONARY VASCULAR TONE AND THE ANESTHESIOLOGIST

M. RAMEZ SALEM* AND GEORGE J. CRYSTAL*

The lung is the necessary link in transporting oxygen from the air to the blood. In this process, the pulmonary capillaries provide the critical air-blood interface. The thinness of the pulmonary capillary wall is conducive to fluid leakage and pulmonary edema, which could impair oxygenation of the blood. The pulmonary capillaries must maintain adequate perfusion, but it is essential that the perfusion is regulated so that gas exchange is not impaired by excessive fluid leakage. This balance is achieved by modulation of pulmonary vascular resistance (PVR), which is brought about by changes in vascular smooth muscle tone in the pulmonary arterioles.

Physiological studies over the last 40 years have led to a better understanding of the factors influencing pulmonary vascular tone. These factors can be divided into gravity dependent and non-gravity dependent factors. As a result of gravitational effects, both blood flow and ventilation increase linearly with distance down the normal upright lung; however, the increase in blood flow is disproportionate to the increase in ventilation. This results in the alveoli at the apex of the lung being relatively underperfused, and the alveoli at the base of the lung being relatively overperfused. The non-gravity dependent factors include passive and active mechanisms. Passive mechanisms are due to changes in lung volume and cardiac output. An asymmetric U-shaped relationship exists between lung volume and PVR. When lung volume is either increased or decreased from the functional residual capacity (FRC), PVR increases. At lung volumes above FRC, the increase in PVR is related to extravascular compression of small intra-alveolar vessels by the surrounding alveoli. Positive end-expiratory pressure (PEEP) increases PVR through a similar mechanism. The increase in PVR below the FRC is due to mechanical kinking of large extra-alveolar vessels. In the atelectatic lung, the mechanism of increased PVR is active hypoxic pulmonary vasoconstriction (HPV) (see below).

The normal adult pulmonary circulation is a low-pressure, low-resistance circuit that accommodates the entire output of the right ventricle. Understanding passive influences in the pulmonary circulation is essential in identifying active vasodilation or active vasoconstriction (Table 1). An increase in pulmonary blood flow (PBF) accompanied by no change or a slight increase in pulmonary artery pressure (Ppa) is consistent with a passive decrease in PVR, secondary to distension and/or recruitment of previously nonperfused pulmonary vessels. A passive increase in PVR would be suggested by a decrease in PBF accompanied by a relatively constant Ppa. However, an increase in Ppa in the face of no change or a decrease in PBF, would imply an increase in PVR due to active vasoconstriction. Conversely, a decrease in Ppa in the face of no change or an increase in PBF would imply an increase in PVR due to active vasodilation. The latter changes are often observed during the administration of sodium nitroprusside. In patients with pulmonary hypertension, where

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The vessels are rigid and less distensible, Ppa sharply increases with any increase in PBF. Increased Ppa and PVR is a universal feature of acute respiratory failure.\(^7\)

The normal pulmonary circulation also responds passively to increases in downstream pressure, i.e., pulmonary capillary wedge pressure, as has been demonstrated in exercising healthy men.\(^8\) Despite marked reductions in the pulmonary pressure gradient, PBF is well maintained by passive reductions in PVR. This passive distension of the pulmonary vasculature, while minimizing resistance to flow, also increases the vulnerability of the lung to fluid filtration from its capillaries, and the formation of edema. An increase in pulmonary venous pressure (Pvp) leading to pulmonary edema, may play a role in the genesis of the adult

### Table 1. Mechanism of change in pulmonary vascular resistance (PVR), as predicted from observed changes in pulmonary blood flow (PBF) and pulmonary artery pressure (Pap).

<table>
<thead>
<tr>
<th>PBF</th>
<th>Pap</th>
<th>Change in PVR</th>
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<tr>
<td>↑</td>
<td>→</td>
<td>Passive Decrease</td>
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<td>Active Decrease</td>
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<td>→</td>
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<td>Active Increase</td>
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*Horizontal arrow indicates no change or small increase or decrease.*
respiratory distress syndrome (ARDS)\(^1,7\).

Three major categories of active mechanisms influence pulmonary vascular tone\(^1,9\): 1) tissue-derived autocrine or paracrine substances. Substances causing vasodilation include nitric oxide (NO), endothelin, and prostaglandin (PGI\(_2\)) and substances causing vasoconstriction include PGF\(_2\), thromboxane and leukotriene. 2) alveolar gases, especially low oxygen (see below), and 3) neurohumoral factors, including circulating catecholamines and catecholamines released by sympathetic nerve fibers and the renin-angiotensin system. The pulmonary vascular endothelium plays a fundamental role as a source of vasoactive substances and as a location for activation or deactivation of blood-borne vasoactive substances. The active control of pulmonary vascular tone is extremely complex and involves multiple mechanisms, both local and remote, interacting in complex fashions. It is beyond the scope of this editorial to discuss these mechanisms in detail. The reader is referred to a more comprehensive review\(^9\).

Hypoxic pulmonary vasoconstriction (HPV) is an adaptive mechanism whereby blood is diverted away from poorly ventilated alveoli to better ventilated alveoli, thus decreasing the shunt flow and protecting PaO\(_2\). Because it is unique to the pulmonary circulation and perhaps the most potent active vascular control mechanism, HPV has been an area of intense investigation since it was initially described in 1946\(^10\). It is present in all mammalian species, and can occur in the whole lung, a lobe, or a segment. The HPV response occurs primarily in the pulmonary arterioles, which are in close proximity to small bronchioles and alveoli and is a function of both alveolar (P\(_{A\text{O}_2}\)) and mixed venous oxygen tension, but P\(_{A\text{O}_2}\) has a much greater influence\(^1,11-13\).

The molecular mechanism underlying HPV remains uncertain, although various theories have been proposed\(^9\). One theory involves a closure of K\(^+\) channels by hypoxia, leading to smooth muscle depolarization, Ca\(^{2+}\) entry, and smooth muscle contraction. A second theory suggests that HPV is initiated by a reduction in oxidative phosphorylation. A third theory proposes that oxygen tension regulates the production of reactive oxygen species, which control transmembrane Ca\(^{2+}\) flux via a direct action on sulfhydryl groups in the Ca\(^{2+}\) channel protein of the vascular smooth muscle cell.

The clinical effects of HPV can be observed in four scenarios in humans. First, HPV is critical for fetal development by minimizing perfusion of the unventilated lung. Second, at high altitudes (or breathing a low oxygen concentration), HPV increases (or even doubles) Ppa, whereas the wedge pressure remains constant\(^1,14\). The increased Ppa enhances perfusion to the apical alveoli, resulting in a higher PaO\(_2\). High altitude pulmonary hypertension is an important component in the development of cor pulmonale\(^15\). Third, in patients with lung disease, during one-lung ventilation, and in cases of mainstem intubation, HPV causes diversion of blood to the non-hypoxic lung, thus minimizing intrapulmonary shunting and normalizing regional ventilation/perfusion relationships\(^1,16\). Fourth, in patients with chronic obstructive lung disease, asthma, or mitral stenosis, the administration of a pulmonary vasodilator can cause inhibition of pre-existing HPV, and decreased PaO\(_2\)\(^1,17\).

Because the pulmonary vessels are highly distensible, any condition that raises Ppa will passively inhibit HPV. This can occur with mitral stenosis, volume overload, hyperthermia, thromboembolism, and use of vasoactive drugs\(^1,18,19\). Pulmonary vasodilator drugs (isoproterenol, sodium nitroprusside, nitroglycerin), infection, and alkalosis can directly inhibit HPV and increase right-to-left intrapulmonary shunting. A selective application of PEEP to only the non-diseased lung can increase PVR and divert blood back into the diseased lung\(^1,20\). Both iv and inhalational anesthetics have been studied for their inhibitory effect on HPV\(^1\). Although the results have not always been consistent, it is generally accepted that iv anesthetics have no effect on HPV, while inhalational anesthetics have a slight inhibitory effect\(^1\).
There are many clinical scenarios in which control of PVR plays a pivotal role in achieving cardiovascular stability. Two will be addressed in this editorial. The survival of neonates with hypoplastic left heart syndrome (HLHS) depends on: 1) a patent ductus arteriosus (PDA) (or the creation of a palliative central shunt) to provide systemic blood flow (SBF), and 2) a balanced level of PVR relative to systemic vascular resistance (SVR), since both pulmonary and systemic circulations are supplied from a single ventricle in a parallel fashion (Fig. 1)\textsuperscript{21-23}. An excessive decrease in PVR causes an increase in PBF at the expense of SBF, a "pulmonary steal" phenomenon. This results in decreases in both systemic and coronary blood flow, leading to myocardial depression, metabolic acidosis, and circulatory collapse despite a high PaO\textsubscript{2} due to the elevated PBF. Conversely, an excessive increase in PVR reduces PBF, leading to reductions in PaO\textsubscript{2}, and ultimately myocardial depression and circulatory collapse, despite initially high systemic and coronary blood flows.

\textbf{Fig. 1}

\textit{Balance between PVR and SVR is essential for survival of patients with HLHS before or after creation of a palliative shunt}

See text for details. Abbreviations: PVR, pulmonary vascular resistance; PBF, pulmonary blood flow; SBF, systemic blood flow; CBF, coronary blood flow; PDA, patent ductus arteriosus.

If PaO\textsubscript{2} is relatively high (PaO\textsubscript{2} >50) in patients with HLHS, decreasing ventilation to allow PaCO\textsubscript{2} to increase (and pH to decrease), generally increases PVR and decreases PBF and PaO\textsubscript{2} \textsuperscript{21}. Lowering FIO\textsubscript{2} and increasing PEEP may also be necessary to decrease PBF, thus paradoxically decreasing PaO\textsubscript{2}\textsuperscript{21}. These measures result in increased SBF. In the presence of low PBF with resultant hypoxemia (PaO\textsubscript{2} <20 mm Hg), hyperventilation to a lower PaCO\textsubscript{2} (20-25 mm Hg), in addition to other measures to decrease PVR, can improve PaO\textsubscript{2} to viable levels (30-40 mm Hg). These maneuvers, although difficult to maintain, are useful in the perioperative period and in the critical care setting in maintaining the balance between PVR and SVR, which is essential for survival of HLHS patients.

Another situation where a delicate balance between the SVR and PVR is necessary is in patients with tetralogy of Fallot (TOF) (pulmonary stenosis or atresia, an overriding aorta, ventricular septal defect, and right ventricular hypertrophy)\textsuperscript{24}. In these patients, right-to-left shunting and cyanosis are worsened by increased right
ventricular outflow tract obstruction, elevated PVR and reduced SVR. Furthermore, increased myocardial contractility due to sympathetic activation or administration of β-adrenergic agonists may promote infundibular spasm, resulting in infundibular shutdown. Factors increasing PVR, including hypoxemia and acidosis, can lead to a further decrease in PBF, an increase in right-to-left shunting, and worsening of hypoxemia. Reduction in SVR also increases shunting across the ventricular septal defect. Sudden episodes of hypoxemia in TOF patients are due to spasm of the right ventricular outflow tract, which results in further decrease of PBF and increased right-to-left shunting. Once initiated, a vicious cycle of increased hypoxemia and acidosis develops, which requires immediate treatment (Fig. 2). Increasing SVR with phenylephrine or another α-adrenergic drug is recommended. In cyanotic pediatric patients with TOF, infusing phenylephrine until systolic arterial blood pressure was increased by 40 mmHg has been demonstrated to raise PaO₂ by an average of 14 mmHg and to reduce right-to-left shunt by an average of 25%. Careful administration of a small doses of β-adrenergic antagonists and enhancing preload can also be helpful. Attempts should be made to decrease PVR by correcting acidosis, decreasing PaCO₂ and adjusting FIO₂.

Fig. 2
Vicious cycle in patients with tetrology of Fallot

See text for details. Abbreviations: SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; RVOT, right ventricular outflow tract.

The manuscript by Mahdi et al. in this issue addresses the effect of moderate hypocapnia in a limited number of patients with elevated PVR following surgery to correct mitral valve stenosis. The findings provided “proof of concept” that hypocapnia is an effective pulmonary vasodilator in these patients. It was demonstrated...
that a 30 min duration of moderate hypocapnia was a simple, safe, and inexpensive technique, which reduced PVR by one-third. The authors concluded that hypocapnia would provide a bridge until pulmonary vascular tone begins to normalize following surgery for mitral valve stenosis. This study provides a springboard for future research to answer pertinent questions. Among them are: Does the reduction in PVR persist if the exposure to hypocapnia is extended beyond 30 min? Does the decrease in PVR vary as a function of the degree of hypocapnia? Is the technique of induced hypocapnia, as an intervention to reduce PVR, applicable to patients with pulmonary hypertension from other causes?
References

Abstract

It is important for anesthesiologists to appreciate the impact of preoperative anxiety in children. Not only does it cause suffering in many children prior to their surgical experience, it has a negative impact on their postoperative recovery and possibly long afterwards. Because of these concerns, continued research is warranted to seek ways of minimizing their fears in the perioperative setting. In this review, we will examine the risk factors for preoperative anxiety, tools for quantifying children and parent’s anxiety, and strategies that may play a part in decreasing preoperative anxiety. Variables, which influence preoperative anxiety in children, include their age, temperament, prior hospital experience and parent coping abilities. This review will also explore issues surrounding parental presence during a child’s anesthesia induction and how understanding child development can enhance their cooperativeness during the preoperative period, especially during anesthesia induction. Non-pharmacological interventions as a means of decreasing pediatric anxiety will be explored. Finally recent trends and new directions will be touched upon.

Introduction

Means of conquering children’s anxiety in a surgical setting has long been sought after. Children requiring anesthesia services for surgery or diagnostic procedures are especially likely to be anxious, as are their parents. In the United States alone, more than 3 million anesthetics are delivered to children annually\(^1\). Many others visit emergency rooms or doctors offices for minor invasive procedures, dental work or diagnostic tests. Pre-procedural and especially preoperative anxiety is a piece of the larger problem of anxiety associated with medical environments in children. Various medical staff, parents and pediatric patients, themselves, strongly desires a better understanding of how to successfully promote a calm and pleasant preoperative experience.

A child’s surgery is often a very significant and memorable event in the life of an entire family but especially the child’s personal history. Unlike other significant events in the child’s life (such as vacation, birthdays, visit to the zoo) this visit has an element of “threat”. The fear of the unknown can be overwhelming.
It is not surprising therefore that up to 65% of children experience significant anxiety associated with the preoperative period².

In addition to its impact on postoperative outcomes, preoperative anxiety is an extremely unpleasant sensation for children. It is experienced in children by feelings of tension, dread, nervousness and uncertainty about their fate. Some may vocalize their fears while others manifest it in behavior such as crying, agitation, and cessation of conversation or play and even attempting to escape from care providers. This is accompanied by significant physiological changes such as increase in heart rate and secretion of stress hormones³. The effect of preoperative anxiety on postoperative outcomes have been recognized in studies dating back 50 years that found a correlation between preoperative anxiety and post-operative maladaptive behavioral changes²,⁴. These include general anxiety, nighttime crying, enuresis, separation anxiety, and temper tantrums⁵,⁷ and can hinder the ability of children to cope with unfamiliar environments such as future medical encounters. Additionally, increases in postoperative pain and emergence delirium⁸ are significant post-operative concerns, which can cause negative behavioral changes. The relationship of increased risk of aspiration or PONV with anxiety in children has not been borne out by studies⁹,¹⁰.

As many as 67% of children may develop postoperative negative behavioral changes including general anxiety, apathy and withdrawal, separation anxiety, sleep disturbances, aggression towards authority, and eating disturbances. Children who exhibit more anxiety preoperatively may be 3 times more likely to exhibit such negative behaviors. Although studies have shown the frequency of these behaviors to decrease rapidly over time, concern remains that in some children this may have long term negative impact on their future healthcare interactions and potentially hinder normal development¹¹. Among the large percentage of pediatric patients who suffer from severe preoperative anxiety, anesthesia induction is known to be the most anxiety provoking part of the preoperative experience⁶,¹². Awake IV placement and parental separation are other vulnerable time points. Therefore, a lot of the research focuses on managing distress at these time points.

Risk Factors and Prediction of Preoperative Anxiety in Children

With an understanding of risk factors for children and parents likely to develop significant preoperative anxiety, it is hoped that these “at-risk” patients can be identified in advance; an appropriate strategy can be directed towards them to reduce the impact of these factors and improve perioperative outcomes¹³.

Child Factors

**Age:** Separation anxiety may be present as early as 9 months and peaks at 1 year. Children age 1-5 are at most risk for experiencing severe preoperative anxiety⁶,⁷.

**Temperament:** Shy or inhibited children and those with a high IQ with poor social adaptive abilities are more prone to anxiety⁷.

**Previous medical encounters:** Negative memories of previous hospital experiences, pediatrician or dentist visits⁷ can last into adolescence¹⁴.

**Attachment style and quality of parent-child relationship:** Beginning infancy an attachment style is developed determined by the quality of relationship with parents. A poorly attended infant may develop poor coping skills in new settings¹⁵.
**Biologically based vulnerabilities:** Children with increased sensitivity to novelty and transition and developmental delay are more prone to anxiety in unfamiliar surroundings.

One study suggested drawings by children in the preoperative waiting room might provide clues to their level of anxiety\(^{16}\).

**Parental Factors**

Children of anxious parents who use avoidant coping mechanisms and of divorced or separated parents are more anxious\(^{13}\). Predictors of increased parental anxiety, itself a risk factor, are gender of the parent (mothers are more anxious), parents of infants, of children who have been through repeated hospitalizations and baseline temperament of the child\(^{13}\). Parents accompanying children have physiological responses (Heart rate variability\(^{17}\), salivary amylase levels\(^{18}\)) that correlate with their children’s preoperative behavior.

**Perioperative Environmental Factors**

In one study, increased levels of anxiety in children was associated with increased number of people in the room at induction of anesthesia, longer waiting time between admission at the hospital and induction of anesthesia, negative memories of previous hospital experiences, and having a mother who does not practice a religion\(^{19}\).

**Stimuli:** Children are found to be less anxious and showed increased compliance during induction when exposed to a single care-provider in a dimmed, quiet operating room with background music\(^{12}\).

**Anesthetic Techniques:** (Inhalation vs. Intravenous induction) Preoperative anxiety may be higher in children who receive an IV before induction\(^{20}\). However there are some advantages at induction of having an IV in situ\(^{21}\). This choice varies greatly with regional practice and patient age.

**Personnel:** Health care professionals can positively or negatively affect the anxiety level of children. Attending anesthesiologists who practice in pediatric settings are better than mothers in predicting the anxiety of children during induction of anesthesia\(^{22}\).

**Assessment of Anxiety in Children and Parents**

Most astute care providers are reasonably good at judging anxiety level of children in the first few minutes of the interview. However, these subjective assessments, even by parents, may be prone to error. Adolescents and older children are most prone to have their anxiety level underestimated by their outer apparent calm\(^{23}\). This age group especially fears waking up during the surgery or not waking up at all\(^{24}\).

For research in pediatric perioperative anxiety, more reliable measures are required. The most popular means of measuring pediatric anxiety has been the “Gold Standard”, "State-Trait-Anxiety Inventory for Children (STAIC)\(^{24,25}\), which is best used with children over the age of 5 years\(^{25}\). It is a self-report questionnaire, takes approximately 5-10 minutes to complete, but may lack practicability in a busy operating room setting\(^{25}\). Over the last decade, the modified-Yale Preoperative Anxiety Scale (m-YPAS) has become the measurement tool of choice for assessing preoperative anxiety\(^{25,26}\). This scale determines a child’s level of anxiety by
evaluating a series of behaviors from calm to severe. The m-YPAS is most appropriate to use prior to anesthesia induction. The Induction Compliance Checklist (ICC) may be a preferable anxiety-measuring tool at the child’s anesthesia induction. For postoperative maladaptive behaviors, the Post-Hospital Behavioral Questionnaire (PHBQ) is widely used as a self-report questionnaire for parents.

Perioperative Adult Child Behavioral Interaction Scale (PACBIS) is a more recent scale for prediction of emergence delirium via preoperative assessment of behaviors, is real-time and has good validation. Another study supports the validity of a numeric 0-10 anxiety self-report scale to assess state anxiety in children as young as 7 yr, which may have advantage by virtue of simplicity.

### Child Development For The Anesthesiologist

An appreciation of the stage of psychosocial development is important to target stage appropriate interventions towards the child. Among the many theories of child development stages, Erikson’s psychosocial developmental stages can perhaps be applied most easily to the perioperative setting.

(See Table 1).

#### Table 1

<table>
<thead>
<tr>
<th>Age</th>
<th>Stage of Psychosocial Development</th>
<th>Suggestions</th>
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<tbody>
<tr>
<td>0-1 Yrs</td>
<td>Building trust (for fulfillment of basic needs)</td>
<td>Soothed by: pacifier, cuddling, rocking, soft spoken voice</td>
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<tr>
<td></td>
<td>Approx. 9 mo. separation anxiety begins</td>
<td>Parental presence at induction of anesthesia (PPIA)</td>
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<tr>
<td>1-3 Yrs</td>
<td>Autonomous / Egocentric. Often state with authority, “I do it”!</td>
<td>Age appropriate, simple explanations</td>
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<td></td>
<td>Sensory aspects important</td>
<td>“Hands-on” in simple language (what will hear, see, smell, feel)</td>
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<tr>
<td></td>
<td>Fear abandonment</td>
<td>PPIA</td>
</tr>
<tr>
<td></td>
<td>Understands more than they verbalize back</td>
<td>Provide simple choices</td>
</tr>
<tr>
<td></td>
<td>Most critical coping skill is PLAY</td>
<td>Distraction</td>
</tr>
<tr>
<td></td>
<td>Time frames not distinguishable</td>
<td>E.g. “We will go home at Lunchtime”</td>
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</table>
4-5 Yrs | Reality and fantasy not distinguishable | E.g. stretcher may be perceived as actually stretching a person. Careful with language medical supplies i.e. say, “finger sticker”; instead of “it’s like a band aid’. Band-aids associated with pain.  
| Most critical coping skill is PLAY | Distraction by Play  
| Like making choices | Flavor on the “mask”  
| Magic & pretend are fun | Allow child to explore basic medical supplies  
| Sensory aspects important | Be current with associations i.e. finger light is like “Buzz Lightyear’s” light. Most don’t know “E.T.”  
| Time frames difficult to understand | Associate with length of favorite show (i.e. “Takes as long two Dora shows”)  
| Separation anxiety | PPLA  
6-12 Yrs | Like to take part in care | Provide choice to help hold anesthesia mask or which finger to place finger sticker  
| Want to be told the truth | Be honest about tastes of medicine or pain on IV insertion  
| Take information literally | Careful with language i.e. “put to sleep” similar to how family dog was put down). This (Propofol) will “burn” interpreted as arm may set on fire  
13-18 Yrs | Age of identity | Can provide more detail about medical procedures  
| Privacy is important | Inquire about teens personal information in private  
| Very self-conscious | May prefer to change into hospital gown behind closed doors  
| Fear waking up during surgery and possibility of death | Verbal Reassurance of safety and monitoring and reversibility of anesthetic “sleep”  

Adapted from: Ref. 31 – 35.

Strategies to Reduce Preoperative Anxiety

Premedication

Premedication forms an important arm of a multipronged strategy and in many practices is often the only means of managing preoperative anxiety in children. This aspect will be discussed in another chapter. This chapter will focus on non-pharmacological strategies.

Management of Preoperative Fasting
Fasting is an essential part of preoperative preparation and is often one of the most uncomfortable aspects for children. Humane and rational management of this necessity (evidence based policies, active communication with parents, monitoring of scheduling delays or changes) will help in reducing unnecessary distress in children.  

**Parental Presence at Induction of Anesthesia (PPIA)**

Protecting one’s offspring from a potential threat is an intense biological instinct that can be observed across boundaries of geography, history, culture, time and even species. It is not surprising that separation from their children, even for medically necessary procedures, is a stressful experience for parents and children. Majority of parents would prefer to stay with their children as long as possible in their perioperative journey.

The following comment, from the mother of one of our patients, illustrates the emotions of many a parent:

“I am a mother of four and would not send my children in there, scared and alone. Some children have a blanket, some a stuffed animal, all in the name of security. There is nothing more safe and secure than the loving look of a mom, the soothing sound of her voice, or the comfort of her arms. I am grateful to be the security my children needed at this very scary time” N.B.

**Does PPIA benefit children, parents, or neither?**

Previous research has shown PPIA to benefit the child during anesthesia induction, promote parent satisfaction and present an anchor of security. PPIA was also shown to promote a smoother anesthesia induction for the child. There remain regional and international differences in acceptance of PPI, for example more anaesthetists in the UK allow PPIA than their counterparts in the US, although there are trends towards increased acceptance. This increase may be credited to increased research efforts and better understanding from the anesthesia team regarding parent’s participation. In addition, parents are increasingly aware of the possibility of PPIA and have raised expectations. For anesthesiologists it remains a challenge to balance their personal and institutional approach to PPIA with the desire of many parents to maximize their involvement. This is further complicated by a paucity of high-level evidence that supports PPIA despite an intuitive expectation it would reduce anxiety in most children. Kain et al did not demonstrate a benefit in either preoperative anxiety, compliance with induction or post operative delirium vs. parent absent induction, while premedication with midazolam was superior to PPIA. In another study there was no incremental benefit of PPIA when added to premedication with midazolam.

Two recent systematic reviews did not favor PPIA over other methods. Reviewers for the Cochrane collaboration summarized their review of 8 trials of PPIA as showing no significant differences in anxiety or cooperation of children during induction except for one trial where parental presence was significantly less effective than midazolam in reducing anxiety. A recent study showed the benefit of parental presence at separation that did not extend to placement of the anesthesia mask.

**Why PPIA may not be effective on its own:** The structure of randomized trials should be considered in appreciation of evidence for PPIA. Randomized controlled trials (RCTs) reflect the results of centers which offer PPIA to all parents. Results may differ where anesthesiologists selectively consider PPIA based on personality characteristics of each child and parent. Secondly allowing parental presence without adequate preparation may have a negative effect, causing more distress if they exhibit behaviors like excessive reassurance, criticism or commands. Therefore, research has turned its focus on the individual factors...
surrounding PPIA like quality and timing of parent-child preparation and what parents actually do while present, rather than simply their presence or absence at induction. PPIA on its own was found to be effective in select circumstances related to the age and baseline anxiety levels of the child and parent. In their review of 568 subjects studied over the course of 7 years, Kain et al observed that calm child-anxious parent combination received the least benefit from PPIA.

**What do parents experience and want:** PPIA can be a stressful experience for parents. Upsetting events for them can be their child in distress, going limp or rolling their eyes and having to leave their child. There is evidence of increased skin conductance levels and rise in heart rates in mothers at PPIA indicating heightened arousal; however, abnormal EKG findings were not observed.

It has been found that parents overwhelmingly prefer PPIA for their child’s subsequent surgery, regardless of their first experience and majority choose PPIA over premedication in subsequent surgeries.

**Objections to PPIA:** Many anesthesiologists are concerned about increased stress on the OR team, reduced efficiency, distraction from the care of patient and teaching of trainees, liability for the parental injury, the possibility that the parent would not want to leave at the appropriate time or may become combative. It seems prudent to allow parents to be present with appropriate disclosure and precautions but not invite parents who do not wish to be present. Each institution should consult with its legal team to formulate a sound policy regarding PPIA. Anesthesiologist anxiety about parental presence at induction decreases significantly with experience and differs with type of practice. Pediatric anesthesiologists and anesthesiologists who routinely take care of children are more likely to allow PPIA.

**Summary:** “No parent should ever be forced to be present for induction of anesthesia, nor should any anesthesiologist be forced into a situation that compromises the quality of care”. PPIA is becoming more widely accepted and may be beneficial with appropriate preparation.

**Other Non-Pharmacological Interventions**

1. **Before the hospital:** The preoperative journey often starts with the child’s pediatrician. This is a good opportunity for pediatricians to develop more awareness of preoperative issues and start educating the parents at an early stage. Communication between the pediatrician and the anesthesia team about the child’s unique needs can be helpful.

2. **The preoperative interview:** The preoperative interview is a routine “behavioral intervention” that is an opportunity for the anesthesiologist to assess the child, develop rapport with the child and family, provide them with a detailed anesthesia plan and provide reassurance that their child will be well protected. The often daunting task of going over the risks of anesthesia in detail is concerning to many anesthesiologists lest it provoke parental and child anxiety. This is not supported by evidence. In fact, the parents who received more detailed risk information were no more anxious than those who did not. Children also deserve (and desire) an age-appropriate explanation of what to expect. An empathetic interview and informed consent requires honesty, expertise, self-confidence, patience and superior communication skills. Parents often fear anesthesia more than surgery. The communication skills of the anesthesiologists (and nurses) are very important in building trust with the family. In a satisfaction survey of parents and children “lack of fear at the moment of being anesthetized, and lack of anxiety on the day preceding surgery, were attributed to the serenity transmitted by the anesthetist and nurses.”
The approach of anesthesiologists and the perioperative team should be customized to the individual child. For example, not all children will require premedication and not all children under a certain age prefer an inhalational induction. The cooperative child may have previously conquered IV placements and is confident in beginning an anesthesia induction in this manner. The cooperative child may need a different inhalational technique than another who is non-compliant.

3. Preoperative information programs: Many approaches can be used to deliver preoperative information to educate children and parents. For example, information leaflets\(^{61}\), interactive books\(^{62}\), videos\(^{63}\), tours of the facility have been shown to have a positive but variable impact on preoperative anxiety. Modeling by videos is more effective if it is facility specific\(^{64}\). An informational Saturday Morning Camp in the UK had favorable effects on preoperative anxiety but significance was limited to the waiting room and the authors did not recommend widespread adoption\(^{65}\).

Giving appropriate information and age-appropriate medium are important. For example, effort should go into researching what parents actually want to know for better results\(^{66}\). Similarly adolescents expressed more satisfaction with an Internet based program\(^{67}\).

Visitation has logistical and cost issues and may have limited usefulness. Coordinating visits with the family’s other obligatory trips to the hospital is advisable to reduce the burden on them. In the age of multimedia telecommunication there are many alternatives to an informational visit.

4. Behavioral Interventions Programs: The ideal behavioral preparation should be effective in reducing anxiety, should be low cost in terms of personnel and time, should be easy to administer (ideally by trained parents) and should not necessitate separate visits to the hospital.

The most effective behavioral interventions are development of coping skills, followed by modeling, play therapy, operating room tour and printed material\(^{68}\). Coping skills can range from simply suggesting deep breathing and counting to promoting distraction activities such as a favorite DVD or handheld game. Distraction is considered a very effective form of coping for younger children\(^{69}\). When anxiety is decreased through preparation and play, children become more confident and cope better with medical procedures.

Kain et al found that an elaborate and costly behavioral preoperative program had limited anxiolytic effects and did not have significant impact on the induction of anesthesia\(^{70}\). More recently a comprehensive family centered approach in the form of the ADVANCE preparation program was shown to be effective in the reduction of preoperative anxiety and improvement in postoperative outcomes like reducing emergence delirium\(^{71}\). However costs were noted to be significant and may preclude widespread adoption.

MacLaren et al have recently demonstrated that a simple behavioral intervention based on exposure (to anesthesia mask) and shaping resulted in increased compliance at induction and has the advantage of being administered by parents in the holding area on day of surgery, thus increasing its application. It may represent an effective intervention in a time and resource-constrained environment (Fig. 1)\(^{72}\).

Fig. 1
The role of child-life specialists (or play specialists in some countries) is worth mentioning. A child life specialist is specifically trained in child development. There are about 4000 certified child life-specialists worldwide.73 The majority of large hospitals in the US staff certified child-life specialists (CCLS) and preparation programs are standard in many pediatric hospitals; however there is a vast degree of variability in approach and program implementation, especially in perioperative settings. The primary role of the CCLS is to provide families and children with individualized psychosocial care that should be tailored to their needs such as age, developmental level and previous experience. The three most important aspects of high quality preparation include the provision of developmentally appropriate information, the encouragement of emotional expression and the formation of a trusting relationship with a healthcare professional. These components remain the principal base of preparation for over thirty years.68 The role of the child life specialist is to promote the child’s confidence and cooperation perioperatively. They use sensory-based preparation for what children will experience preoperatively, and this is proven to be an effective means of managing preoperative anxiety as opposed to verbal information alone. Most importantly, child life specialists promote play as a means of helping children cope with the often intimidating perioperative setting. Play allows children to relax and reduces their anxiety, which then allows them to become less defensive.

In our practice, the CCLS have significantly reduced the need for premedication and have generated increased parent satisfaction. They have also allowed the anesthesia team to function in an efficient manner by allowing them more time to concentrate on clinical concerns. The comparative effectiveness and economical impact of a CCLS based preparation program should be an interesting area for further study.

In summary, preparation programs based on behavioral interventions have had a mixed record of success suggesting that preparation is not as simple as it appears.37 The details of a child’s prior hospitalization experiences, age, and timing relative to surgery are important variables. Preparation should be provided at least
5 days in advance for children > 6 years and no more than a week in advance for children < 6 years. Individualized coping skills training rather than modeling are more beneficial to children who have prior hospital experiences as they are not provided with new information and may actually have negative effects with re-exposure to medical equipment\(^{26,37}\).

5. Distraction Activities and Play: Various distraction strategies have been found to be useful in reducing preoperative anxiety. The importance of allowing children to get involved in or carry on play activities cannot be overestimated. Play comes naturally to children and is often their favorite activity. Providing an environment conducive to play activities\(^{76}\), toys\(^{77}\) or using existing handheld game technology to make the environment less threatening (Fig. 2), has been shown to reduce anxiety\(^{78}\), enhance cooperation of children with medical procedures\(^{79}\) and anesthesia induction. The PediSedate\(^{®}\) device is an interesting combination of a child friendly gaming console and nitrous oxide delivery device, well received by older children, but is associated with increased PONV. Even readily available smart phones (e.g. iPhone)\(^{80}\) and web-based entertainment (you Tube)\(^{81}\) can be used as distraction aids. Devices like video-goggles have the dual advantage of distraction and shielding the view of a harsh-looking operating room (Fig. 3).

In our practice, our CCLS facilitate play to be carried through to the Operating room and during induction of anesthesia. (Fig. 4 and 5).

*Fig. 2 & 3*
The presence of medically trained clowns in the perioperative area has been shown to be an effective measure though acceptance by the operating team has been a challenge. However in another study anxiety at mask placement was not reduced.

Music therapy has been effective in adults as an anxiolytic but its impact on children has been modest. Interactive music therapy may relieve anxiety on separation and entrance to the operating room but appears less effective during the induction of anesthesia.
6. Complementary and Alternative Medicine Strategies: Some interesting work has shown the effectiveness of hypnosis in children as well as use of acupressure at the extra-1 point. Hypnosis alleviated preoperative anxiety, especially during induction of anesthesia and reduced behavioral disorders during the first postoperative week. Another study demonstrated that auricular acupuncture in anxious mothers was effective in reducing maternal anxiety and enhancing the child’s cooperation at induction.

7. Child Friendly Environment: The design of the operating room suite, color scheme, flow process and décor are important tools to enhance feelings of comfort in children and reduce the sense of threat (Fig. 6).
Recorded maternal voice was effective in reducing perioperative anxiety and emergence phenomenon during cardiac catheterization in children\textsuperscript{88}.

8. Behavioral Interventions Targeting Care Providers: An intriguing area of study is to target perioperative provider behavior, which have shown to influence preoperative anxiety in children. Desired behaviors (coping promoting) by parents and medical staff include approaches like distraction, humor, and non-procedure related talk. Undesired behaviors (distress promoting) include excessive reassurance, empathetic comments, apologies and criticism and may actually increase anxiety. In a multicenter pilot study, educational interventions to target specific provider behaviors resulted in increases in “coping promoting behaviors” and reduction in children’s anxiety levels\textsuperscript{89}.

**Recent Trends and Future Directions**

It is increasingly recognized that addressing preoperative anxiety should be a multimodal effort. Provider behavior may be another contributory factor amenable to positive change. Easy access to economical portable entertainment technology has increased the options for distraction and play to enhance child’s coping skills. Virtual reality may provide another modality\textsuperscript{90}. Attention has focused on attempting to improve postoperative behavioral recovery by reducing preoperative anxiety. There are indications that such efforts may also influence clinical recovery, such as reducing postoperative pain\textsuperscript{91}.

The child-parent combination is “joined at the hip” and requires a comprehensive approach by the medical facility to address its collective need for information, empathy and reassurance. The child-parent unit is a package deal and addressing the child’s preoperative anxiety requires addressing both their concerns. A
successful program will require a commitment to this comprehensive approach by the entire facility including staff training, architectural design (child-friendliness) and layout (access to play space). In a recent article, Chorney et al argue for such an approach including families in the entire perioperative experience of the child-family unit, not just the preoperative period. “.. Families are an integral part of the perioperative care team and should be treated as such. Efforts should be made to establish collaborations by openly communicating, developing a shared vision for the care of the child, and building a cohesive care team that includes healthcare providers and family members throughout the perioperative period” 37. In order for this to become the standard of care, pediatric and general hospitals need to commit significant resources and anesthesiology residency programs need to include this philosophy in the education of future (and re-education of current) practitioners.

Conclusions: Promoting a positive perioperative experience is best achieved through comprehensive, age appropriate preparation of the child, as well as the parents, for what to expect. To be successful, a family centered approach has to encompass the entire journey of the child through the perioperative period and has to utilize all suitable resources, personnel and strategies. Anesthesiologists are likely to remain important conductors of this multifaceted effort. Anesthesiologists taking care of children should recognize the risk factors, and individualize management of perioperative anxiety in a family-centered environment.
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PREMEDICATION OF THE CHILD UNDERGOING SURGERY

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The preoperative period is a stressful event for the majority of individuals undergoing surgery. This is especially true in the pediatric patient and is related to a limited understanding of the nature of the illness and the need of surgery by young children. Pharmacological and behavioral interventions are used to treat preoperative anxiety in children and their parents.

Among the different results that may be achieved with premedication such as amnesia, optimization of preoperative conditions and prevention of physiological stress, the primary aim in children is anxiolysis. Almost 50% of children show signs of significant preoperative fear and anxiety 1. It has been reported that there are correlations between heart rate, blood pressure, and behavioral ratings of anxiety 2. In order to alleviate physiological and psychological effects of preoperative anxiety in children, most anesthesiologists use either parental presence or sedative premedication, since separation from parents and induction of anesthesia are considered the most perioperative stress inducing phases. Both approaches are considered appropriate choice of interventions. Anesthesiologists who allow parental presence during induction of anesthesia use sedative premedication least frequently, and vice versa 3,4.

Historically, it is interesting to document that the initiation of the practice of pediatric outpatient surgery was associated with major modifications such as discontinuation of the use of preoperative sedation in this patient population. This was thought to be necessary because the most popular premedicant drugs available at the time were long acting (e.g., morphine and Nembutal), delayed recovery, and increased the incidence of postoperative vomiting. In addition, there was no available oral premedication agent. This practice resulted in compromising the psychological welfare of many children for the sake of efficiency and rapid discharge. Availability of oral midazolam premedication is the main reason pharmacological sedation regained popularity in pediatric anesthesia, especially in ambulatory practice.

Parental Presence or Premedication?

Early studies suggested reduced anxiety and improved patient cooperation if parents were present during induction 5,6. The majority of parents prefer to be present during induction of anesthesia regardless of the child's age or previous surgical experience 7, and also regardless of their experience with prior parental presence or premedication of their child in the case of repeated surgery 8.

Concerns regarding parental presence on induction of anesthesia include a negative behavioral response to stress in some children when a parent is present and an upsetting experience to the parents, especially if watching their child going limp or when leaving their child after induction 9,10. This has been demonstrated by an increase in heart rate and skin conductance levels in mothers 11. Oral midazolam has been shown to be more

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effective in reducing a child's anxiety than parental presence and parental presence combined with oral midazolam was not superior in reducing a child's anxiety than sedation alone\textsuperscript{12}. It has been shown that parental presence during induction of anesthesia is mostly beneficial in children older than 4 years of age who share a “calm” baseline personality with the accompanying parent\textsuperscript{13,14}. Limitations to these controlled studies may be that randomization in subject recruitments may not reflect the everyday practice of anesthesiologists who carry an individual approach in dealing with their patients and parents.

If parental presence during induction is deemed to be in the child's best interest, a clear explanation that describes what the parent can expect to happen during the periinduction period can significantly decrease parental anxiety and increase their satisfaction, which may be reflected in the child’s behavior\textsuperscript{15-17}. Predictive risk factors for children who would probably benefit from sedative premedication include children between the ages of 2 and 6 years, who are shy and inhibited, those who have a history of prior stressful medical encounters and those accompanied by an anxious parent\textsuperscript{18,19}. In the extremely anxious child, premedication would be indicated in order to avoid a traumatic anesthetic induction, with the possibility of postoperative psychological disturbances\textsuperscript{20}.

**Premedication**

The major objectives of preanesthetic medication are to decrease the stress response with preservation of hemodynamic parameters, facilitate anesthesia induction and produce amnesia. The child's age, body weight, drug history, allergic status and underlying medical or surgical conditions are factors to be taken into consideration prior to administration of premedication. In most cases, medications administered without a needle are more pleasant for children, the family and the care team. Oral premedication does not increase the risk of aspiration pneumonia\textsuperscript{21}.

Different medications may be used for premedication.

**Benzodiazepines**

**Midazolam:** The most commonly used sedative premedicant in the preoperative holding area is midazolam\textsuperscript{22}. It should be administered under direct supervision with the patient placed in a closely monitored bed space in the preoperative holding area. Major attributes of midazolam are its availability as an oral preparation and its short onset and offset of action. As a standard syrup preparation, it exists in both an open and closed ring structure, the proportion of which is pH dependent. At lower pH values there is a greater proportion of drug in the open ring and at higher pH values there is a reduction in the proportion of the drug in the open ring configuration. Since only the open ring formulation is lipophilic and physiologically active, bioavailability is highly sensitive to changes in pH. Therefore, the combination of any “home made” diluents with the intravenous midazolam formulation could significantly alter both the absorption rate and the bioavailability\textsuperscript{23}. The most common oral dose used is 0.5 mg/kg and ranges from 0.25 to 0.75-1 mg/kg have been described. Higher doses of midazolam (1 mg/kg) appear not to offer any additional benefits, and may cause more side effects. Commercially prepared midazolam formulation is rapidly absorbed with patients demonstrating a satisfactory degree of sedation and anxiolysis within 10 minutes of consumption with a higher percentage at 20 minutes. A bitter taste has been described after oral and nasal administration. The dose of oral midazolam should be adjusted in children taking depressants or inducers of the cytochrome oxidase system,
such as anticonvulsants or barbiturates.

Other routes of administration of midazolam are used; these are the nasal, rectal, intramuscular and intravenous routes. The dose of midazolam is 0.025 to 0.1 mg/kg intravenously. The bioavailability [and suggested dose] of midazolam is 0.9 [0.1 to 0.2 mg/kg] after intramuscular injection, 0.57 [0.2 mg/kg] after intranasal, 0.4 to 0.5 [1 mg/kg] after rectal, and 0.3 [0.25 to 0.75 mg/kg] after oral administration. A sublingual route of administration [0.2 mg/kg] has also been described 24-30.

After intravenous administration of midazolam, the time to peak central nervous system (CNS) electroencephalographic effect is 4.8 minutes. It is preferable to wait this interval of time prior to administering an additional dose of midazolam in order to avoid over sedation. Intravenous midazolam is best reserved for children who already have a functioning IV line to avoid the added trauma of venipuncture.

Peak plasma concentrations of midazolam after intranasal administration occurs in only 10 minutes, however, discomfort has been associated to this route secondary to irritation. Also, a preservative-free midazolam is recommended when using this route of administration since intranasal midazolam with preservative has been shown to have neurotoxic effects in an animal model 31.

There is synergism between propofol and midazolam on \( \gamma \)-aminobutyric acid (GABA) receptors 32. Oral midazolam decrease the infusion requirements of propofol by a third during a propofol-based anesthetic 33. After premedication with oral midazolam (0.5 mg/kg), in children 1 to 3 years of age post adenoidectomy, emergence and early recovery were delayed with no change in discharge times after induction of anesthesia with propofol, and maintenance with sevoflurane 34. Spontaneous eye opening and discharge time were delayed as compared with placebo after 25 minutes of sevoflurane anesthesia 35. However, extubation, awakening and discharge times were not affected after sevoflurane anesthesia in children 1 to 10 years receiving the same dose of oral midazolam 36.

Midazolam has the advantage of producing anterograde amnesia. Memory usually becomes impaired within 10 minutes after oral midazolam 37. This has a beneficial effect in children requiring repetitive interventions.

Midazolam, like other benzodiazepines increases the threshold for central nervous system toxicity with seizures; however the threshold for cardiovascular toxicity is unchanged. Thus, after premedication with midazolam or a benzodiazepine, cardiovascular collapse after regional anesthesia toxicity may occur unassociated with CNS symptoms of toxicity.

Secondary and adverse effects to midazolam may include a paradoxical effect with behavioral changes and agitation and hiccups. This may occur independently of the mode of administration, i.e. rectal, nasal, or oral ketamine, 0.5 mg/kg, IV has been shown to reverse the agitation 38.

**Lorazepam:** may be administered orally, intravenously, or intramuscularly and is metabolized by the liver to inactive metabolites. The intravenous formulation has been reported to be neurotoxic in neonates 39. Lorazepam has a slow onset and offset of action, and therefore is better used for inpatients. It has good amnestic properties and less tissue irritation than diazepam. The usual dose is 0.05 mg/kg administered orally or intravenously to older children; however a dose of 0.025 mg/kg has been adequate to decrease preoperative anxiety 40.

**Diazepam:** has a greater fat solubility than midazolam and a faster CNS effect after intravenous administration (1.6 min); however it is metabolized to desmethyldiazepam with a pharmacologic activity equal to the parent compound 41. Diazepam is an unpopular choice as a preoperative premedicant in young children.
because of immature liver function that would lead to a prolonged half life. The average oral dose for premedicating healthy children with diazepam ranges from 0.1 to 0.3 mg/kg. When administered rectally, diazepam appears to be less effective than rectal midazolam. The intramuscular route is not recommended because it is painful and absorption is erratic.

**Barbiturates**

Not commonly used for premedication in children since the availability of short acting benzodiazepines. A major disadvantage is hyperalgesia which can induce agitation in children with pain. Intravenous methohexitol has a relatively shorter elimination half-life (3.9 ± 2.1 hours) than thiopental (9 ± 1.6 hours) because of a faster hepatic metabolism. Methohexitol, in a rectal dose of 20 to 30 mg/kg, may result in sleep/sedation in 15-20 min but at the risk of producing hiccups, apnea, airway obstruction, laryngospasm, seizures, in addition to an unpredictable systemic absorption and possible allergic reaction. An increase in absorption because of rectal mucosa abnormality may lead to cardio-respiratory arrest. Contraindications to methohexitol include porphyria, hypersensitivity and temporal lobe epilepsy. The dose of rectal thiopental and onset of action are similar to methohexitol.

**Nonbarbiturate Sedative**

Chloral hydrate is an orally administered nonbarbiturate (20 to 75 mg/kg with a total maximum dose of 2 g). It is devoid of analgesic properties and has a bitter taste. Its principal advantage is that it can be administered orally or rectally with a relatively good sedation within 30 to 45 minutes. Its use is less frequent than midazolam as a premedicant because of its slow onset and long elimination half-life. Its use is not recommended in neonates and patients with liver disease because of impaired metabolism, and the potential accumulation of toxic metabolites leading to metabolic acidosis, renal failure, and hypotonia. The active metabolite of chloral hydrate, trichloroethanol, has a long half life in toddlers and in preterm infants (39.8 ± 14.3 hours). Therefore, there is a risk for residual drug effect and prolonged sedation or re-sedation. Airway obstruction may occur in children with enlarged tonsils. Deaths after chloral hydrate sedation have been reported. Concerns for potential carcinogenicity with chronic administration exist as well as irritation of the skin, mucous membranes, and gastrointestinal tract, possibly in relation to its metabolism to trichloroacetic acid.

**Phenothiazines**

Promethazine (0.25 to 0.5 mg/kg intravenously, intramuscularly, or orally) has the advantage to possess several beneficial effects such as being an antihistaminic (H1-blocker), an antiemetic, anti-motion sickness, and an anticholinergic in addition to being a sedative. However, it is not a popular premedicant drug in pediatric ambulatory anesthesia because of dystonic reactions reported with its use and because of its long elimination half-life (8 to 12 hours) and an insufficient effect when prescribed alone.

**Ketamine**
Is a phencyclidine derivative that antagonizes the N-methyl-D-aspartate (NMDA) receptor. The principal action of ketamine is due to the central dissociation of the cortex from the limbic system, providing good sedation and analgesia while preserving upper airway muscular tone and respiratory drive. Ketamine also relaxes the smooth musculature of the airway stimulated by histamine and has its application in case of potential risk for bronchoconstriction. It is recommended to administer an antisialogogue (atropine, glycopyrrolate) with ketamine in order to decrease the amount of oral secretions that may occur and to decrease the risk of laryngospasm. Hallucinations during recovery from ketamine may occur mostly in older children although oral ketamine has been reported to reduce emergence delirium. Co-administration of benzodiazepines or subsequent administration of general anesthetic agents reduces the incidence of hallucinations to approximately 4%53. Recovery of patients who have received ketamine in a quiet environment with the least stimulation helps decrease the incidence of undesirable effects such as hallucinations, nightmares, and delirium. The most common adverse reaction to ketamine is postoperative vomiting, which occurs in 33% of children54. The dextro-isomer of ketamine has more potent analgesia and reduced incidence of side effects55.

Intravenous ketamine has a fast onset of effect (<1 min.). Duration of action of a single IV dose is 5 to 8 minutes (α-elimination half-life of 11 minutes and a β-elimination half-life of 2.5 to 3.0 hours)56. Ketamine is administered in very low doses intravenously (0.25-0.5 mg/kg) or intramuscularly (1-2 mg/kg) either alone or preferably in combination with low-dose midazolam (0.05 mg/kg) along with atropine (0.02 mg/kg) for sedation. The dose of ketamine needed to prevent gross movement in infants younger than 6 months of age is four times greater than in children 6 years of age57. Bioavailability of ketamine is approximately 93% after intramuscular administration. The intramuscular route of administration is very useful for children who are uncooperative, refuse oral sedation and become combative. These children become adequately calm in around 3 minutes and accept a mask inhalation induction of anesthesia. There is no documentation of prolongation of the hospital discharge times after IM ketamine administration (2 mg/kg) even after brief surgical procedures and a minimal likelihood of delirium or bad dreams during recovery58. However, the combination of intramuscular ketamine (2 mg/kg) and midazolam (0.1 to 0.2 mg/kg) may prolong recovery and discharge times after brief ambulatory procedures59. A larger dose (4 to 5 mg/kg) sedates children within 2 to 4 minutes, and a dose of 10 mg/kg usually produces deep sedation. Larger and repeated doses are associated with hallucinations, nightmares, vomiting, and a prolonged recovery from anesthesia. Acute tolerance to ketamine has been reported.

Ketamine has also been administered also via oral, nasal, and rectal routes. After oral administration and nasal administration, bioavailability is 17% and 50% respectively.

Oral ketamine alone and in combination with midazolam has been used for premedication in healthy children and those with congenital heart defects. Sedation is usually achieved after a dose of 5 to 6 mg/kg of oral ketamine in most children within 12 minutes, the depth of sedation is sufficient to obtain intravenous access in more than half of the children. Larger doses may prolong recovery from anesthesia. The combination of oral midazolam and ketamine is synergistic in its efficiency for preoperative sedation. The combination of oral ketamine (3 mg/kg) and midazolam (0.5 mg/kg) does not seem to prolong recovery time for procedures longer than 30 minutes60.

Nasal transmucosal ketamine at a dose of 6 mg/kg is also effective in sedating children within 20 to 40 minutes before induction of anesthesia. Only preservative free ketamine should be given nasally to avoid neurotoxicity, the 100 mg/ml concentration is preferable to minimize the volume administered in the nose61.

Rectal ketamine administration has a bioavailability of 25% and can result in an unpredictable effect.
Rectal ketamine (5 mg/kg) produces usually anxiolysis and sedation within 30 minutes of administration.\textsuperscript{62} It is of note that ketamine may produce increases in intracranial pressure (ICP) as a result of cerebral vasodilatation, it also increases CMRO\textsubscript{2}; therefore its administration should be avoided in children with intracranial hypertension. Administration of ketamine also may not be of choice in any child with a history of psychiatric or seizure disorder because of its psychotropic and epileptogenic effects. Ketamine may be potentially dangerous in the presence of eye trauma since increase in intraocular pressure has been documented with its use.

Studies in mice and rats have correlated ketamine treatment with increased neuronal apoptosis during rapid synaptogenesis after birth. The clinical importance of these findings to humans is unclear.

**Opioids**

Opioids may be used as a preanesthetic medication to children with preoperative pain; however opioid-related side effects such as respiratory depression, dysphoria, pruritus and nausea/vomiting are to be taken into account when administering opioids. If opioids are used in combination with other sedatives such as benzodiazepines, the dose of each drug should be appropriately adjusted to avoid serious respiratory depression.

Neonates are very sensitive to the respiratory depressant effects of opioids, and they are rarely used to premedicate this age group.

Fentanyl may be administered by parenteral, transdermal, nasal, and oral routes. A “lollipop” delivery system, oral transmucosal fentanyl citrate (OTCF) is more accepted by children than other routes as a premedicant. Fentanyl is strongly lipophilic, and is readily absorbed from the buccal mucosa with an overall bioavailability of approximately 30-50\%.\textsuperscript{63} The optimal dose as a preanesthetic medication with minimal desaturation and preoperative nausea appears to be 10 to 15 μg/kg. Children begin to show signs of sedation within 10 minutes after receiving this dose. Recovery from anesthesia after a premedication of 10 to 15 μg/kg of oral fentanyl is similar to that after 2 μg/kg intravenously. Doses greater than 15 μg/kg are not recommended because of opioid side effects, particularly occasional respiratory depression. The incidence of the opioid associated side effects is increased when the interval between completion of “lollipop” and induction of anesthesia is prolonged.\textsuperscript{64,65} OTCF is now primarily indicated for the treatment of breakthrough cancer pain. Fentanyl has also been administered nasally (1 to 2 μg/kg) but primarily after induction of anesthesia as a means of providing analgesia in children without intravenous access.

Sufentanil is 10 times more potent than fentanyl. Several instances of reduced chest wall compliance have been reported in children after nasal sufentanil, as well as a higher incidence of nausea and vomiting and a prolonged discharge time when compared to nasally administered midazolam.\textsuperscript{66} These potential side effects and prolonged hospital stay after nasal sufentanil makes it an unpopular choice for premedication.

Morphine sulfate may be administered intramuscularly (0.1 to 0.2 mg/kg) or intravenously (0.05 to 0.1 mg/kg) or orally. Absorption may not be adequate when given rectally.

Meperidine is a synthetic opioid with a more rapid onset of action and reduced duration of action than morphine. The usual dose for premedication in children is 1 to 2 mg/kg intramuscularly 1 hour before induction. Meperidine may also be administered intravenously and orally. An oral dose of 1.5 mg/kg may be used to sedate patients before anesthesia. Meperidine is metabolized to normeperidine and central nervous
system excitation (seizures, twitches and tremor) may result from accumulation of normeperidine after chronic or large doses administration\textsuperscript{67}.

Tramadol is a weak $\mu$-opioid receptor agonist whose analgesic effect is mediated via inhibition of norepinephrine reuptake and stimulation of serotonin release. Intravenous tramadol (1.5 mg/kg) given before induction of general anesthesia has been as effective as local infiltration of 0.5% bupivacaine (0.25 ml/kg) for ilioinguinal and iliohypogastric nerve blocks for pain control, but associated with a higher incidence of nausea and vomiting\textsuperscript{68}.

Butorphanol is a synthetic opioid agonist-antagonist with properties similar to those of morphine that can be administered nasally. A dose of 0.025 mg/kg administered nasally immediately after the induction of anesthesia was shown to provide good analgesia after myringotomy and tube placement at the expense of increased incidence of emesis at home compared with children who received nonopioid analgesics such as acetaminophen\textsuperscript{69}.

Codeine is a commonly prescribed oral opioid, which must undergo O-demethylation in the liver to produce morphine to provide effective analgesia. Five to 10 percent of children lack the cytochrome isoenzyme (CYP450 2D6) required for this conversion and therefore do not derive analgesic benefit. Codeine can be given orally or intramuscularly but should not be administered intravenously because of the risk of seizures. The usual oral dose of oral codeine is 0.5 to 1.5 mg/kg with an onset of action within 20 minutes and peak effects between 1 to 2 hours. Codeine has an elimination half-life of 2.5 to 3 hours. The combination of codeine with acetaminophen is effective in relieving mild to moderate pain.

\textbf{$\alpha_2$ Agonists}

Clonidine, an $\alpha_2$ agonist, causes dose-related sedation by its effect in the locus ceruleus through its inhibition of adenylate cyclase. The plasma concentration peaks at 60 to 90 minutes after oral administration and at 50 minutes after rectal administration\textsuperscript{70}. The need to administer clonidine 60 minutes before induction of anesthesia makes its use impractical in most clinical settings. An oral dose of 3 $\mu$g/kg given 45 to 120 minutes before the surgery produces comparable sedation to that of diazepam or midazolam\textsuperscript{71}. Clonidine acts both centrally and peripherally to reduce blood pressure and therefore it attenuates the hemodynamic response to intubation. It is usually administered in combination with atropine. In children undergoing tonsillectomy, the group who received oral clonidine, 4 $\mu$g/kg, showed more intense anxiety on separation and during induction than the group who received midazolam (0.5 mg/kg) with reduced mean intraoperative blood pressures, reduced duration of surgery, anesthesia, and emergence, and decreased need for supplemental oxygen during recovery but greater postoperative opioid requirements, greater pain scores, and excitement in the clonidine group. Time to discharge, postoperative nausea/vomiting, and 24-hour analgesic requirements were similar in both groups\textsuperscript{72}.

\textbf{Antihistamines}

Not commonly used because their sedative effects are variable. Diphenhydramine is an H\textsubscript{1} blocker with mild sedative and antimuscarinic effects. The dosage for children is 0.5 mg/kg intravenously, or intramuscularly\textsuperscript{73}. Although the duration of action is 4 to 6 hours, it does not appear to interfere with recovery.
from anesthesia.

Hydroxyzine has antiemetic, antihistaminic, and antispasmodic effects with minimal respiratory and circulatory changes. It is usually administered IM at a dose of 0.5 to 1.0 mg/kg.

**Anticholinergic Drugs**

Anticholinergic agents were commonly used in the past to prevent the undesirable bradycardia associated with some anesthetic agents (halothane and succinylcholine), to minimize the autonomic vagal reflexes, and to reduce secretions. Current inhalational anesthetics are not associated with bradycardia and do not stimulate salivary or tracheobronchial secretions, therefore, the routine use of an anticholinergic drug is not generally needed. In the majority of cases, anticholinergics are given after intravenous access is established.

Atropine (0.02 mg/kg) and scopolamine (0.01 mg/kg) both have CNS effects, although the sedating effect of scopolamine is 5 to 15 times greater than atropine. Atropine is more commonly used and is a better vagolytic agent than scopolamine, whereas scopolamine is a better sedative, antisialagogue, and amnestic. Glycopyrrolate is the only agent that does not cross the blood-brain barrier, so it does not cause confusion. When compared to atropine, it is less effective in attenuating bradycardia during induction. The central sedative effects of both atropine and scopolamine may be antagonized with physostigmine. Preoperative administration of oral atropine or oral glycopyrrolate does not alter the incidence or degree of hypotension during induction of anesthesia.

Anticholinergic agents are very useful as an adjuvant to ketamine anesthesia because of their antisialagogue and central sedative effects.

The recommended doses of anticholinergics are scopolamine, 0.005 to 0.010 mg/kg, atropine, 0.01 to 0.02 mg/kg and glycopyrrolate 0.01 mg/kg IV, IM.

**Topical Anesthetics**

Topical anesthetic creams may represent an attractive alternative to intradermal infiltration, but sometimes with some limitations.

EMLA cream (eutectic mixture of local anesthetic, Astra Zeneca, Wilmington, DE) is a mixture of two local anesthetics (2.5% lidocaine and 2.5% prilocaine). One-hour application of EMLA cream to intact skin with an occlusive dressing provides adequate topical anesthesia for an intravenous catheter insertion. However, EMLA causes vasoconstriction and skin blanching, making intravenous cannulation more difficult. Methemoglobinemia may occur secondary to prilocaine. However, a 1-hour application of EMLA cream and a maximum dose of 1 g did not induce methemoglobinemia when applied to intact skin of full-term neonates younger than 3 months of age.

Ametop is a topical local anesthetic (4% tetracaine) with onset time of 30- to 40-minute. The advantages are the absence of vasoconstriction or skin blanching, and there is no risk of methemoglobinemia.

ELA-Max (4% lidocaine) decreases pain associated with intravenous catheter insertion after only a 30-minute application. In addition, ELA-Max blanches the skin to a lesser extent and dilates veins better than EMLA cream. There is no risk of methemoglobinemia with this formulation.

The S-Caine Patch (ZARS, Inc., Salt Lake City, UT), is a eutectic mixture of lidocaine and tetracaine (70
mg of each per patch) that uses a controlled heating system to accelerate delivery and analgesic effect of the local anesthetic. An application time of 20 minutes lessens pain associated with venipuncture in children and is associated with only mild and transient local erythema and edema and no skin blanching. Methemoglobinemia has not been reported with this formulation.

Lidocaine iontophoresis uses an impregnated electrode, current generator, and a return pad to carry ionized lidocaine through the stratum corneum. It provides similar pain relief for insertion of intravenous catheters in children as EMLA cream but requires training and equipment for application. It may cause a stinging pain during current application and potential skin burns from the electrodes.

In summary, the primary goal of premedication in children is to ease the induction of anesthesia by facilitating a smooth separation from the parents. Other pharmacological effects (amnesia, prevention of physiologic stress, reduction of total anesthetic requirements, decrease risk of aspiration, of acidic stomach content, and analgesia) may also be achieved. Special considerations for patients with deteriorating mental status, with airway obstruction or patients with hemodynamic instability/intolerance to hypercapnia (such as those with significant increases in pulmonary artery pressure/pulmonary arteriolar resistance) or with systemic organ failure should be taken into account prior to administration of premedication. In these cases, parental presence may be the preferable choice. The major effect of premedication is to allay anxiety, but has the potential to produce sedation and should always be administered with caution under supervision and close monitoring. Tools for administration of supplemental oxygen, ventilation support and resuscitation should be readily available.
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EMERGENCE AGITATION IN CHILDREN

- A Review -

VIVIANE G. NASR * AND RAFAAT S. HANNAHALL **

Introduction

Eckenhoff et al first described emergence agitation (EA) in the early 1960’s. Children anesthetized with ether, cyclopropane, or ketamine undergoing tonsillectomy, thyroidectomy and circumcision experienced crying, thrashing and disorientation during emergence from anesthesia1.

Today, approximately 4 million children undergo anesthesia each year and EA has been identified as a significant problem in children recovering from anesthesia with a reported incidence ranging between 10-80%2-5. EA manifests with restlessness and disorientation and may cause injury to the child, disruption of the surgical site and dressing, drains, or even removal of intravenous catheters. Extra nursing care especially in the PACU is needed. Medication given to treat EA may delay discharge from the PACU and sometimes from the hospital.

Since 1960, this topic has been studied and investigated with multiple comparative studies of inhalational and intravenous anesthetics, effects of adjuvants to general anesthesia; and different assessment tools have been described. In this review, we will discuss the most recent updates on the topic and point out the controversies present despite ongoing clinical research.

Definition

The term “emergence agitation” has been interchangeably used with “emergence delirium (ED)” and “excitement” in order to describe an irritable, uncooperative, and inconsolable child upon emergence6,7. However there are differences in definitions and clinical presentations of agitation and delirium.

“Agitation”, which is simply excessive motor activity, is quite common in the postoperative period in children as well as in adults. It is a nonspecific symptom resulting from any type of internal discomfort including pain and anxiety. Agitation resulting from pain or anxiety is relatively easily treated with reassurance and the appropriate use of analgesics and benzodiazepines.

“Delirium”, however, is more difficult to diagnose, prevent, or treat, and the clinical outcome of patients with delirium is much different. Delirium, like anxiety, is characterized by an unpleasant alteration of mood. Unlike anxiety, delirium is an acute state of confusion accompanied by cognitive impairment (perceptual
disturbances and hallucinations).

Unfortunately, the distinction of cognitive impairment, which is critical to making the proper diagnosis and prescribing appropriate therapy for EA, is difficult to differentiate in children. Therefore the terms emergence agitation and emergence delirium are used interchangeably in the literature.

When present, EA occurs within the first 30-minutes of recovery from anesthesia, is usually self-limited but can last up to 2 days. The incidence ranges between 10-80%. Many studies have been done in order to determine the etiology of EA. These point to surgical and patient related factors, as well as anesthesia related factors such as rapid emergence and type of anesthetic.

**Assessment tools of emergence agitation**

EA have been widely described, several factors have been implicated and studied and controversies continue to exist. Comparing studies have been difficult due to the lack of a uniform definition of emergence agitation and the lack of a universal assessment scale. Therefore, many tools have been described and studied in order to define, grade the “agitation” and treat accordingly. As many as 16 different scales and two visual analog scales have been used. None of these tools can differentiate between pain and emergence agitation. Przybylo et al devised tool that assesses behaviors separate from pain-induced agitation. Also, Sikich et al developed the Pediatric Anesthesia Emergence Delirium (PAED) scale incorporating cognitive and agitation assessments and proved its reliability and validity (Fig. 1). However, they did not define the threshold for ED making it difficult to calculate its incidence. Aouad et al by assessing ED using two different scales found that the threshold score of 10 on the PAED scale was the best discriminator between presence and absence of agitation correlating with the agitation and nonagitation scores on the four-point scale. In contrast to all previous studies, Pieters et al did not find a difference in ED following propofol versus sevoflurane anesthesia when measured by the PAED scale attributing this to a low cutoff >10 on the PAED scale. Bajwa et al have compared three different emergence delirium scales and have found a reasonable correlation between all three scales despite the individual limitations. More importantly the subjective assessment by an experienced anesthesiologist is highly likely to score positive on all three scales.

![Fig. 1](PAED scale)
Factors contributing to emergence agitation

Several factors have been implicated in the etiology of emergence agitation and their effect has been extensively studied in the literature through randomized clinical trials.

1-Patient and parent related:

Age:

Aono et al have shown in 1997 that preschool boys aged 2-6 years have higher rate of EA compared to schoolboys. This finding was embraced by most studies focusing on EA. The authors attributed this to rapid awakening and psychological immaturity. In fact, Martini’s commentary addresses the role of brain maturation and suggests a role of physiologic development to the susceptibility of the young age group to delirium.

Preoperative anxiety; patient and parent:

Preoperative anxiety has been associated with increased postoperative agitation. Kain et al in a retrospective database search of 791 children have shown that high levels of preoperative anxiety in the child are predictive of the development of adverse postoperative behavior including emergence delirium. The odds of ED increased by approximately 10% with each increment of 10 points in children’s state anxiety score. No clear relationship was demonstrated between parental anxiety and ED. However, in a recent study, Fortier et al have shown that parental anxiety is a risk factor for high levels of child anxiety across the perioperative setting, from the preoperative holding area, up to two weeks postoperatively and therefore could be a contributing factor to ED.

Kain et al have shown recently in a prospective controlled study recruiting 241 children that preoperative anxiety is related to increased postoperative pain and behavioral changes. However, it remains to be determined if this relationship is an association or a cause-effect.
Temperament of the child:

Premedication or preparation programs as discussed later in this review can modify preoperative anxiety of the child and the parent. However, temperament of the child including emotionality, activity, sociability and impulsivity cannot be modified. Voepel-Lewis et al found that low adaptability in children is associated with increased incidence of EA. Kain et al have also shown that ED was higher among children who are more emotional, more impulsive and less sociable. Therefore this innate temperament of the child undergoing anesthesia might cause him to react differently to the outside environment and therefore could cause EA.

Parental presence during recovery:

Most of the studies focus on the preoperative anxiety of the parent and the presence of the parent prior to the anesthetic and the effect of these two factors on the child’s EA. However, only few studies mention the effect of the parent as the child awakens in the postanesthesia care unit (PACU). Weldon et al have shown that the incidence of EA decreased as the parent joined the child in the PACU. Demirbilek et al observed that the parental presence decreased the agitation despite the presence of surgical pain. Aouad et al have also related the low incidence of EA in children undergoing inguinal hernia repair under caudal block to the parental presence in the PACU in addition to the lack of pain. The positive effect of parental presence in all above mentioned studies was only a noticeable observation and was not the studied outcome. Many hospitals today welcome early parental presence in the PACU as the child is recovering from anesthesia. And therefore, a prospective study rating EA prior to arrival of the parent and after their arrival to the PACU would be of interest.

2-Surgical procedure:

Type of procedure:

Surgical procedures involving the ears, eyes, tonsils, thyroid and urological surgeries have been associated with higher rates of EA. When Eckenhoff at al first described the EA in 1961, he attributed the increased incidence among otolaryngologic procedures to the “sense of suffocation”. Later, in 2003, Voepel-Lewis in a prospective study has shown that the otolaryngologic procedures are an independent risk factor for EA. The increased incidence during ophthalmologic procedures could be related to the distortion or lack of ability to see the outside environment.

Pain:

Most of the above mentioned procedures are painful and pain has been acknowledged as a major risk factor for EA. Several studies have been done in order to study the causal effect of pain and EA and to decrease the incidence of EA by treating pain with different modalities including NSAID, ketorolac, α2-agonist such as clonidine, dexmedetomidine, regional anesthesia including caudal blocks and narcotics. The incidence of EA in these studies has decreased after adequate pain control compared to controls but was not abolished. This suggests the presence of EA despite adequate pain control. In fact, Cravero et al have found that the incidence of EA was higher in sevoflurane anesthetized patients compared to halothane in children undergoing nonpainful interventions such as MRI. Therefore, pain cannot be pointed out as the sole contributing factor to EA.
EMERGENCE AGITATION IN CHILDREN: A REVIEW

3-Inhalation and intravenous anesthetics:

Sevoflurane’s high incidence of emergence agitation has led to numerous studies evaluating the incidence of emergence agitation following inhalation and intravenous anesthetics. It was found that sevoflurane is not the only anesthetic implicated in agitation. Desflurane as well as isoflurane have been shown to have a comparable incidence ranging between 50% and 80%3,9,31. In fact, the electroencephalogram changes occurring in patients under sevoflurane are similar in patients under isoflurane and desflurane32. However, most studies have shown that sevoflurane causes more agitation than halothane with different electroencephalogram changes4,13,33. Kuratani et al have shown in a meta-analysis identifying 23 studies comparing sevoflurane and halothane that emergence agitation occurs more frequently with sevoflurane34.

The rapid emergence following sevoflurane has been speculated to be the cause of EA. Awakening in an unfamiliar environment could cause EA. Patients who have decreased ability to cope with environmental stresses tend to become more agitated. Studies have compared sevoflurane and propofol on the quality of recovery35-37. Cohen et al compared emergence from sevoflurane and propofol, which allows a fast recovery38. They found that rapid emergence from propofol was smooth and pleasant compared to sevoflurane and concluded that EA was not related to the speed of recovery. In fact, delaying emergence by stepwise decrease of sevoflurane did not reduce the incidence of EA as shown by Oh et al39.

Similarly, Grundmann et al have shown that in children, TIVA with remifentanil and propofol is a well-tolerated anesthetic method, with a lower perioperative heart rate and less postoperative agitation compared with a desflurane-N₂O based anesthesia40.

Therefore, EA is not related to the rapid recovery but could be related to the intrinsic property of inhalation anesthetics.

4-Premedication:

The possible association of midazolam, a commonly used premedicant in children with ED has been a controversial topic. Few studies have shown that midazolam decreases agitation postoperatively following sevoflurane2 while others have shown no effect or even noted an increase in agitation34,41. We can suggest that midazolam may decrease agitation by its residual sedative effect at the end of surgery for short procedures as noted by Lapin et al or by decreasing anxiety score preoperatively2.

Other premedicant drugs has been used and compared to midazolam. Oral clonidine 4 mcg/kg given thirty minutes prior to sevoflurane anesthesia induction in preschool children is associated with a significant reduction in EA compared to midazolam 0.5 mg/kg (25% vs. 60%)27.

Premedication with melatonin have been proven to be superior to midazolam in reducing excitement following emergence from sevoflurane and similar in decreasing preoperative anxiety42. In contrast to the above mentioned drugs, oxycodone, a long acting opioid did not decrease agitation in children who received sevoflurane anesthesia but decrease the frequency in children who received halothane43.

5-Adjuvants to GA including pharmacological and nonpharmacologic tools:

- Pharmacological adjuvants:
Several drugs have been used as adjuvants to general anesthesia, aiming to decrease the incidence of emergence agitation\textsuperscript{44,45}.

Propofol delays or modifies emergence and decreases emergence agitation depending on the time of administration. Being a short acting medication, propofol given at induction could not prevent emergence agitation\textsuperscript{46}. Aouad et al as well as other studies have shown a decrease in EA following propofol administration (1 mg/kg) at the end of surgery, as plasma concentration of propofol can be effective\textsuperscript{11}.

Fentanyl, $\alpha_2$-agonists including clonidine and dexmedetomidine, ketamine have been shown to be effective measures in decreasing the incidence of EA.

Fentanyl is a potent opioid, which can decrease EA following sevoflurane and desflurane anesthesia by its high efficacy on preoperative analgesia as well as its sedative effect\textsuperscript{47-50}. Cravero et al have shown that fentanyl 1 mcg/kg IV given 10 minutes before the discontinuation of the anesthetic in patients undergoing nonpainful procedure such as magnetic resonance imaging decreased the incidence of EA from 56\% to 12\%\textsuperscript{45}. Inomata et al studied the effect of fentanyl infusion on the intubating conditions as well as emergence agitation in children anesthetized with sevoflurane\textsuperscript{30}. They recommended a bolus of 2 mcg/kg followed by an infusion of 1 mcg/kg/hr for a smooth emergence. Intranasal fentanyl 2 mcg/kg for moderately painful procedures can also decrease agitation\textsuperscript{51,52}.

Dexmedetomidine, a selective $\alpha_2$-agonist has sedative, analgesic and anxiolytic effects after IV administration\textsuperscript{53}. Isik et al as well as two other studies have shown a reduced incidence of emergence agitation ranging between 4.8\% and 17\% with no hemodynamic effects after IV administration of 0.3-1 mcg/kg dexmedetomidine after induction of anesthesia\textsuperscript{29,30,54}.

Similarly, because of its sedative and analgesic effects, clonidine 2-3 mcg/kg IV after induction decreases agitation on emergence down to 0\%-10\% as documented respectively by Bock et al and Kulka et al.\textsuperscript{28,55} Bock et al have also noted that the effect of clonidine is independent of the route of administration: intravenous or caudal\textsuperscript{28}. In fact $\alpha_2$-agonists decrease EA by their analgesic effect as well as by decreasing the anesthetic requirements.

Ketamine, a N-methyl-D-aspartate receptor antagonist, produces both analgesic and opioid sparing effects when used at low doses\textsuperscript{56-58}. Dalens et al showed that administration of 0.25 mg/kg of ketamine at the end of the MRI in children reduced agitation with no delay in discharge\textsuperscript{56}. In fact, Lee et al compared ketamine 0.25 mg/kg and 0.5 mg/kg showing similar incidence of EA however less pain score with the higher dose of ketamine\textsuperscript{57}.

It has also been shown that tropisetron, a 5HT3 antagonist, decreases emergence agitation compared to placebo (32\% vs. 62\%) however; the mechanism of action is unclear as described by Lankinen et al.\textsuperscript{59} In summary; most adjuvants studied have decreased ED postoperatively in painful and nonpainful procedures through their analgesic and sedative effects. A recent meta-analyses by Dahmani et al have shown that propofol, opioids such as fentanyl, pain prevention, ketamine and $\alpha_2$-agonists have a preventative effect on ED while midazolam and serotonin inhibitors did not have a prophylactic effect\textsuperscript{44}. However, comparison between the different drugs using the same scale remains of benefit for more definitive conclusion.

- Nonpharmacologic tools including child life and preoperative preparation programs:

Holding the child and physical restraint may be necessary sometimes to protect the child. A very effective method is reuniting with the parent/caregiver during awakening. It is also important to maintain a quiet environment for the child.
Demirkilek et al was not able to decrease the incidence of EA further by the use of fentanyl if the parents and the child’s anxiety were controlled\textsuperscript{23}.

**Relationship between EA and long-term postoperative maladaptive behaviors:**

Long-term maladaptive behavior can occur following anesthesia in children. It has been hypothesized to be related to the hypnotic depth, the duration of the anesthetic, type of anesthetic as well as the incidence of emergence agitation. Kain et al suggests that patients with emergence delirium are seven times more likely to have new onset postoperative maladaptive behavioral changes including eating problems, sleep disturbances, separation anxiety and apathy\textsuperscript{18,60}. This is in contrast to Sikich and Lerman who were unable to find a statistically significant relation between emergence agitation and negative postoperative behavioral changes\textsuperscript{10}.

Recently, Faulk et al revealed no correlation between the length of time under deep hypnosis defined as BIS\textless45 and the incidence of EA or negative postoperative behavioral changes\textsuperscript{61}.

In addition, there is no conclusive relationship between the type of anesthetic and the maladaptive behaviors. In fact, Keany et al have shown no relationship between sevoflurane and maladaptive behavior and Kain et al found no difference in behavior between children exposed to sevoflurane or halothane\textsuperscript{62,63}.

Kain et al have reported that 54\% of all children undergoing general anesthesia exhibit negative behavioral responses 2 weeks after the surgery and continues up to 6 month in 20\% and up to one year in 7\%\textsuperscript{16}. He reports in a later study the benefit of premedication with midazolam 0.5 mg/kg on decreasing this incidence during the first week as decreasing preoperative anxiety decreases the incidence of emergence agitation\textsuperscript{60}. In view of these results, we cannot establish a theory associating emergence agitation and long-term maladaptive behavior or type of anesthetic and behavioral changes.

**Prevention and treatment:**

As previously described in details, numerous medications have been studied to prevent or reduce emergence agitation in children. No one effective method has been shown to be highly superior. It is very difficult to compare studies as each uses different assessment tools, type of surgical procedure, or even anesthetic techniques.

However, it is no doubt that a young anxious preschool child undergoing a painful surgical procedure without adequate pain control will most likely suffer from emergence delirium. As studies are ongoing trying to discover the underlying causes or trying to treat and prevent the occurrence of emergence agitation, it is the role of the anesthesiologist to recognize patients at risk, involve the parents preoperatively as well as postoperatively and use adjuvants drugs as deemed necessary.
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POSTOPERATIVE MALADAPTIVE BEHAVIORAL CHANGES IN CHILDREN

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Abstract

Induction of anesthesia can be a very stressful period for a child and his family and can be associated with increased risk of psychological disturbances. These disturbances are categorized as preoperative anxiety, emergence delirium and postoperative behavioral changes. Several tools have been developed to measure these psychological manifestations as well as the baseline personality traits of these patients.

Postoperative negative behavioral changes, such as sleep and eating disorders, separation anxiety, temper tantrum, aggression toward authorities, may occur in up to 60% of all children undergoing general anesthesia. Several studies found a strong association between these postoperative behavioral changes, the distress of the child on induction and his individual personality characteristics, although a cause-effect relationship could not be determined. Understanding the risk factors for behavior changes helps us determine the best way for prevention and treatment of these changes in the perioperative period.

Introduction

Induction of anesthesia may be the most stressful procedure a child experiences during his hospitalization. Psychological and behavioral changes can be observed in three different aspects: preoperative anxiety, emergence delirium and post operative behavioral changes. These behavioral changes have been a target of interest for more than 60 years. In 1945, Levy reviewed the records of 124 postoperative children referred for behavior problems and found that some of them did not have any preoperative history of emotional difficulties. In a retrospective study of 612 children undergoing otolaryngological operation, Eckenhoff identified the association between unsatisfactory anesthesia inductions and postoperative negative personality changes. This led to the recognition of the importance of addressing children’s anxiety in the postoperative period. Although these are important landmark studies, measurement tools to assess the level of anxiety and classify behaviors were not validated. Since then, various investigators developed new measurement modalities validated in several studies with good reliability.

Negative behavioral changes observed postoperatively include separation anxiety, sleep disturbance, aggression toward authority, temper tantrum, and eating problems, and have been described in as much as 50-60% of children undergoing surgery. They can be associated with poor perioperative outcomes, including

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delayed hospital discharge and poor parental satisfaction, and if they persist for an extended period time, they can interfere with the child’s emotional and cognitive development. Understanding the risk factors for behavior changes helps us to determine the best way for prevention and treatment of these changes in the perioperative period. Several studies have been conducted to determine this relationship with contradictory results.

We will review the risk factors for maladaptive behaviors and suggested interventions.

**Characteristics of maladaptive behaviors**

Common behavioral problems after surgery include nightmares, waking up crying, sleep disorders, disobeying parents, separation anxiety, and temper tantrums. More serious behavioral changes, such as new-onset enuresis are uncommon. Interestingly, some children experience positive behavioral change following surgery, which may be attributed to the treatment of their medical conditions.

Maladaptive behaviors subside with time. Kain et al. found that 67% of children had new negative behaviors on the first day after surgery, 45% on day two, and 23% at two weeks after surgery, but these changes could persist for up to 6 months in 20% of children and for up to one year for 7.3% of children.

Some children may have several surgical procedures during their childhood. Whether or not repeated surgical experience has a cumulative effect on the development of maladaptive behaviors is unknown.

**Behavioral instruments**

Behavioral instruments that are used to assess both the predictor variable and the primary end point must be properly validated and reliable. Until now various measurement modalities have been developed to assess anxiety and behaviors, and include:

*The State-trait Anxiety Inventory (STAI)*

This self-reported anxiety instrument contains two separate 20-item subscales that measure trait (baseline) and state (situation) anxiety. It is used to assess situational anxiety of parents immediately after being present for anesthesia induction of their child. This is the gold standard for assessing anxiety in adults and has been used with good validity and reliability.

*The modified Yale Preoperative Anxiety Scale (mYPAS)*

This is an observational state anxiety measurement for young children, containing 27 items in 5 categories (activity, emotional expression, state of arousal, vocalization, and use of parents). However, it does not include non-anxiety behaviors of children and adults. It has excellent reliability and validity for measuring children’s anxiety in the preoperative holding area and during induction of anesthesia.

*The Induction Compliance Checklist (ICC)*
This is an observational checklist, previously developed by Kain et al., containing 10 negative behavioral groupings that describe child’s anxiety, fear and negative behaviors during induction of anesthesia with good reliability. However, it does not assess a child’s non-anxiety distress behaviors or any adult behaviors.\textsuperscript{12}

\textit{The Perioperative Adult Children Behavioral Interaction Scale (PACBIS)}

This instrument was developed to assess perioperative children and parents behaviors that might predict postoperative problematic behavior and emergence excitement. It uses a 5-point rating scale to evaluate perioperative behaviors in real-time on six dimensions (child coping, child distress, parent coping promoting, parent distress promoting, staff coping promoting, and staff distress promoting). Coping promoting behaviors include nonprocedural talk to children, distraction, praising, encouragement, humor, and commands to use coping strategy. Distress promoting behaviors include excessive reassurance, criticism, apologies, giving inappropriate control to the child and empathic comments. Inclusion of coping behavioral assessment might render behavioral intervention amendable to improve overall perioperative outcome. This test has good concurrent validity and good reliability.\textsuperscript{5}

\textit{The Post-Hospitalization Behavioral Questionnaire (PHBQ)}

This is a parental, self-reported questionnaire consisting of 27 items in 6 domains: general anxiety, separation anxiety, sleep anxiety, eating disturbances, aggression against authority, and apathy/withdrawal. It is used to evaluate maladaptive behavioral responses in children after anesthesia and surgery. It has a good profile of reliability and validity.\textsuperscript{13}

\textit{The Emotionality, Activity, Sociability, Impulsivity (EASI)}

This temperament scale is a parental reported instrument that assesses four temperament categories (emotionality, activity, sociability, and impulsivity) in children and is widely used in the literature. Good reliability and validity data are available for this instrument.\textsuperscript{14}

\textbf{Risk factors for postoperative, maladaptive behavioral changes} \\

\textit{Age}

Postoperative behavioral issues seem to be present in younger children. Eckenhoff found children less than 3 years of age to be more at risk.\textsuperscript{3} Vernon found that children aged 6 months to 4 years had more postoperative negative behaviors than older children.\textsuperscript{15} Consistently, recent studies showed similar findings.\textsuperscript{4,7,16}

\textit{Temperament and personality}
Impulsive children (i.e. high EASI score for impulsivity) have an increased risk of general anxiety and separation anxiety at 2 weeks postoperatively, as well as children with poor social adaptability, children who are shy and inhibited, with higher intelligence, and with increased parental anxiety4.

**Anxiety exhibited in the preoperative holding area**

It is estimated that about 70% of all children exhibit significant stress and anxiety before surgery[4]. Reasons for this behavioral response include the child’s perception of the threat of bodily discomfort, or harm, the threat of being separated from parents, of unknown and strange environment, of uncertainty of what is acceptable behavior, and the threat of losing control and autonomy[7]. Several studies support the association of preoperative anxiety and postoperative maladaptive behavioral changes[4,6,18,19], but this finding was challenged by several other studies[1,20]. Tripi et al. found that even though anxious children have a significantly increased incidence of distress on emergence, they were no more likely than children without emergence distress to manifest long lasting evidence of continued psychological changes when studied at 1 and 4 weeks post operatively[20].

**Parental anxiety**

The association between parental anxiety and negative behavioral changes has been described[1,19,21].

**Pain**

The association of pain and postoperative behavioral changes has been a subject of controversy. Initial investigations by Kain et al. as well as by other groups denied this correlation[1,4]. But with better pain evaluation and assessment of causal factors, subsequent studies showed an association between preoperative anxiety, postoperative pain and postoperative behavioral problems[22]. In a study of children 5 to 12 years old undergoing elective outpatient tonsillectomy and adenoidectomy, preoperative anxiety was associated with increased pain postoperatively and a higher incidence of sleep and behavioral problems[22]. There is no study that shows the direct cause-effect relationship of postoperative pain with the occurrence of postoperative behavioral problems[23]. However, it is unethical to under-treat pain and study the subsequent incidence of postoperative behaviors. Given that pain is undertreated postoperatively in many children[24], it would be important to emphasize the importance of postoperative pain treatment. Reduction of pain severity has the potential of decreasing maladaptive behaviors.

**Length and type of hospitalization**

Outpatient surgery settings is associated with less post operative behavioral changes than inpatient settings, and the length of hospitalization beyond 4 days can influence such behavioral changes in comparison to shorter stays of 2-3 days[1,7,25].

**Anesthetic induction**
Whether the type of anesthetic medication affects the incidence of postoperative maladaptive behaviors is an important issue to be investigated.

Foesel and Reisch evaluated the role of anesthetic induction agents (sevoflurane versus halothane) on the occurrence of negative behaviors postoperatively by reviewing patients charts as well as sending questionnaires to parents postoperatively. They enrolled patients younger than 8 years of age who had minor ENT surgery in most cases. There was no difference in the frequency of postoperative negative behaviors between halothane and sevoflurane in patients under 4 years, whereas patients above 4 years of age who had sevoflurane induction had more frequent behavioral issues. One of the criticisms of this study is the possible bias induced by the prolonged time lag of 6 to 24 months between the dates of anesthesia and when parents answered questions.

In a double-blinded, randomized, controlled trial including children aged 3 to 10 years, the incidence of emergence delirium, maladaptive postoperative behavioral changes, and sleep disturbances did not differ between halothane and sevoflurane induction groups. However, this study did not include patients younger than 3 years of age, who are considered as a high-risk group for postoperative negative behaviors. Based on the available data, it is reasonable to use sevoflurane as an induction agent. Some studies suggested that emergence delirium and new-onset postoperative maladaptive behavior changes are closely related. The odds ratio of having one or more new-onset postoperative maladaptive behavior changes is 1.43 for children with marked emergence delirium when compared with children with no symptoms of emergence delirium, although this correlation was not reproducible in other studies.

Kotiniemi et al. evaluated the effect of the mode of induction of anesthesia on anxiety and subsequent behavioral problems in 90 children, 2 to 7 year old undergoing ENT surgery. They randomly allocated patients to intravenous thiopentone, inhaled halothane, or rectal methohexitone induction. Behavioral changes were detected in 59% of patients in the thiopentone group, 50% of patients in the halothane group, and 58% of patients in the methohexitone group, but children in halothane group had more negative memories of induction. There is no evidence to say one mode of induction is superior to the other.

Surgery

Kain et al. evaluated patients 1 to 7 year old undergoing elective outpatient surgery (ENT surgery, general surgery, genitourinary surgery) and who had a mask induction of anesthesia using halothane. They found that genitourinary surgery was associated with the most negative postoperative behavioral changes and pressure-equalizing tube placement was associated with the least postoperative negative behavioral changes. However, the difference was not statistically significant. Whether the trend observed reflected the degree of postoperative pain is not clear. The earlier meta-analysis done by Vernon et al. did not find the association between surgical procedures and the incidence of postoperative behavior changes.

Interventions

The initial investigations about postoperative behavioral changes were mainly found in pediatric and psychology literatures, till they recently became a hot topic in pediatric anesthesia. Actually the preparation of a child and his family for surgery falls into the domain of pediatric anesthesiologists, and focuses mainly on reduction of preoperative anxiety in the hope of reducing long term effects. These measures include sedative
premedication, parent presence during induction, and preoperative preparation programs.

**Premedication**

The effect of midazolam on postoperative behavioral changes has been better studied as compared to other sedatives. Kain et al. found that midazolam premedication had a positive effect on decreasing the incidence of behavioral changes at postoperative days 1-7, although this effect decreased over time and at 2 weeks post operatively, there was no difference between the midazolam and the placebo group. Postoperative behavioral problems most reduced by the intervention (midazolam) were separation anxiety and eating disturbances. Another study found similar results, with a significantly reduced incidence of postoperative behavioral changes in the midazolam premedication group at 2 weeks. Interestingly, a study by McGraw et al. showed an opposite result; where children in midazolam group significantly exhibited increased negative behavior at one week compared with those in the control. However, the interpretation of this study is rather difficult because the data were collected from two separate hospitals, which reflects the results from different study protocols. Certainly, midazolam may not be beneficial to all patients and further studies need to point the potential patient population who may not benefit from premedication. Interestingly, the study by Finley et al. provides some insight into this issue. They compared anxiety at induction between impulsive and nonimpulsive children with or without midazolam premedication. Impulsive, midazolam-treated children showed no anxiolytic benefit relative to impulsive children in the placebo group. In contrast, nonimpulsive children in the midazolam group benefited from the anxiolytic effects relative to nonimpulsive children in the placebo group, suggesting that midazolam premedication is most helpful in children with anxiety and least helpful for children with impulsive temperament.

The major concern about routine premedication is its potential adverse effects and the delay in recovery and discharge. However, the majority of studies showed that recovery times were not significantly increased by preoperative midazolam administration.

**Parent presence**

The effect of parent presence on postoperative behavior was evaluated. One group investigated the value of parental presence during emergence from anesthesia as soon as the patient was separated from the ventilator but did not find a decrease in the incidence or the severity of emergence distress behavior in children. The presence of parents in the PACU has been studied as well and was found to have no effect on crying in the PACU, but have some long term effect: negative behavior changes 2 weeks postoperatively occurred more frequently in the parent absent group than the parent present group.

**Family program**

Age appropriate information and preparation for surgery has been described in the medical literature since the 1950s. These techniques vary and have evolved along the years, from simple preoperative instruction, to more demonstrative shows with books, movies, puppet therapy, to play therapy and the possibility of active interaction and role playing with the help of a child life specialist who can teach the children relaxation and
coping techniques.\textsuperscript{37}

Most of the hospitals in the US offer some sort of preoperative behavioral programs to children and their parents in the hope that this will benefit patients coming for surgery, by getting them familiar with the new and potentially anxiety-provoking environment, and would eventually lessen their anxiety. Closer investigation about the efficacy of such programs showed that the benefits are not uniformly distributed on all patients’ population, but differs according to age group, the duration of the hospitalization, the severity of the medical condition, previous experiences, as well as the patient’s personal temperament and personal coping strategies and the program offered. Furthermore, some studies suggested a negative effect of some preparation techniques on children.

In 1975, Melamed compared 2 groups of pediatric patients undergoing surgery under general anesthesia and who received a typical preoperative counseling followed or not by watching a film “Ethan Has an Operation”, which demonstrates a child going through the experiences of being hospitalized for an operation. Analysis of the data showed that the movie was more effective in alleviating anxiety on all measures of transitory and situational anxiety at both the preoperative and postoperative assessments, and at a follow up examination 3-4 weeks following discharge.\textsuperscript{37} On the other hand, in a study evaluating the benefit of a preparation book illustrating a considerable amount of information about the procedure, the equipment and the personnel involved, it was found that children exposed to this book had an increased incidence of behavioral disturbance 1-month postanesthesia. This was mostly true in the group of children undergoing shorter procedures, but not those having longer procedures. These authors then concluded that the mode of preparation should be tailored to the severity or complexity of surgery.\textsuperscript{1}

Kain et al. evaluated the effectiveness of a behavioral preoperative preparation program on alleviating the anxiety of children and their parents in the perioperative period. In a study of 143 children undergoing outpatient surgery, they found that behavioral preparation program was not uniformly effective.\textsuperscript{38} Children older than 6 years of age and who received the preparation at least 5 to 7 days prior to surgery benefited from the intervention. In contrast, the program had a negative effect on children younger than 3 years of age, and may be a result of their inability to distinguish fantasy from reality.

The timing of the preparation program relative to the day of surgery was identified as a significant variable. Children 6 years and older were found to be least anxious if they participated in the program more than 5 to 7 days prior to surgery and were most anxious if the program was given one day prior to surgery. Previous investigations also have suggested that older children may benefit from a longer interval between preparation and the date of the procedure. Although the ideal timing in respect to surgery has never been determined, a minimum of one week seems necessary for reduced anxiety in older children. Some authors suggest that if the preparation cannot be done at least one week prior to surgery, no preparation is more advantageous than having it done 1 or 2 days before the intervention.\textsuperscript{38,39}

Surgery center personnel should consider these factors and individualize their prescription of preparation programs for children and families undergoing surgery.

An additional challenge was the group of patients with previous hospital experience. The preparation programs do not provide them with new information, and may actually sensitize them. It is therefore suggested that these patients have an alternative individualized program with more coping skills training and actual practice, tailored to their previous experiences.\textsuperscript{40}

Further studies were conducted to evaluate the effectiveness of these programs in alleviating anxiety at
several points during a child’s hospitalization. In a study designed to compare several degrees of preparation, from simple to extensive: simple information based program during an OR tour, to adding a videotaping as a modeling-based program, to adding a coping based program provided by a child life specialist, it was found that children and parents who received the extensive preoperative preparation program exhibited lower levels of anxiety. But the beneficial effects of this preparation were limited to the preoperative period and the separation from the parents, without being significant at the induction of anesthesia or in the postoperative period.

Conclusion

Management of preoperative anxiety should be a part of the perioperative management of children, as it has been shown in different studies to impact on the occurrence of long-term postoperative behavioral changes. Several factors have been associated with a higher incidence of postoperative behavioral changes, and include the younger age of the patient, his personality and impulsivity, previous hospital or anesthesia experiences, and parental anxiety.

The role of midazolam as a sedative premedication has been well established and shown its efficacy in reducing children’s anxiety, but not in controlling impulsive behaviors. Parent presence at induction of anesthesia is another mode of alleviating induction anxiety and is gaining popularity among pediatric anesthesiologists and is the preferred method when parents are given a choice. Although it is not uniformly efficacious, it provides good parental satisfaction level. Family programs and preoperative preparation are evolving as well, and they are offered to most of children undergoing anesthesia in the United States. Most importantly is to individualize the care of each patient, taking into account all the possible causal factors, previous individual and parental experience of child, in addition to the best judgment of the anesthesiologist.
References

PERIOPERATIVE MANAGEMENT OF THE CHILD WITH BEHAVIORAL DISORDERS

VANDA YAZBEK KARAM* AND HANANE BARAKAT**

Abstract

Behavioral disorders can be a normal part of development of a child, or secondary to extraordinary life stresses or associated with a child’s inherent disorder. In those children, each hospital visit represents a major challenge for the child, his parents and the hospital staff. Hence, a coordinated approach with a clear plan should be made in advance to minimize child’s perioperative stress and to deliver a high quality service.

Introduction

Children with behavioral disorders are likely to require surgery because of coexisting health problems ranging from dental procedures to complex neurosurgery for treatment of epilepsy. In those children, each hospital visit represents a major challenge for the child, his parents and the hospital staff. Hence, a coordinated approach with a clear plan should be made in advance to minimize child’s perioperative stress and to deliver a high quality service.

Undesirable behavior can be a normal part of development; a child’s ability to understand and interact with the environment is constantly evolving. To learn more about the world, a child experiments with ways of interacting with it. Most often, children test the reactions of the people to whom they are closest, their parents1. However, behavioral problems associated with normal childhood development must be distinguished from challenging behavior associated with more complex causes. Challenging behavior is defined as “culturally abnormal behavior of such intensity, frequency or duration that the physical safety of the person or others is placed in serious jeopardy”2. Aberrant childhood behaviors can be secondary to extraordinary life stresses. Children living under any condition that seriously threatens healthy and successful transition through a developmental stage are likely to pose serious behavioral problems. This applies to children who witness violence, are members of communities that have experienced a catastrophic event, are exposed to continuous marital discord, have a chronic illness, have a chronically ill sibling or who don’t feel wanted3,4. The presence of chronic diseases (CD) during childhood such as chronic renal

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disease, diabetes, inflammatory bowel disease, cancer, and sickle cell disease, significantly increases the risk of emotional and behavioral disorders. Although many CD are considered rare in childhood, it has been estimated that they affect approximately 15% of the pediatric population. These disorders can be associated with the neurological alterations inherent to the diagnosis itself. However, they can be essentially associated with the innate difficulties of living with a CD. The prevalence of mental disorders in pediatric patients with chronic kidney disease undergoing conservative treatment and hemodialysis is 52.6%. When compared to normal population, children with chronic idiopathic urticaria showed more psychiatric disorders (70.4% vs. 29.6%).

In addition to childhood behavioral problems stemming from normal development and extraordinary life stresses, a third general category involves problems caused by disorders inherent to the child. Attention deficit disorders are the most common and well known, but conduct disorders, depression, pervasive developmental disorders, and other psychiatric diagnoses may manifest during childhood. About 3-5% of children and 10-15% of adolescents will experience psychiatric disorders. Psychiatric disorders have their origins in neurobiologic, genetic, psychological, or environmental sources. Hence, the development of challenging behavior is greatly influenced by person-and environment-oriented factors, which often interact with each other. Examples of these factors are not only the age, gender and level of intellectual disability of persons, but also poor adaptive and social skills, psychological stress, inadequate problem-solving skills, impaired language, socioeconomic deprivation, negative life events, secondary disabilities and psychiatric disorders. Most studies report prevalence rates of challenging behavior among persons with intellectual deficiency between 10 and 20%, while some authors report substantially higher rates. The more severe the disability, the higher the likelihood of the presence of these behaviors. Examples of challenging behavior include verbal and physical aggression, property damage and destructiveness, disruptive and antisocial behavior, overactivity, temper tantrums, screaming, stereotyped and repetitive behavior, general delinquency, and self-injurious behavior, like head punching, self-biting, skin picking and hitting against hard objects or other body-parts. The most prevalent forms of aggression are punching/slapping/pulling (50%), kicking (24%). However only 0.7% of people with learning disability are considered at risk of causing harm to others. Challenging behaviors have a negative impact on persons with intellectual deficiency and their environment, because they increase the risk of reduced quality of life, stressful events, the need for costly residential care and are obstacles to social integration. Moreover, because of their recurrent character, challenging behaviors tend to become a lifelong challenge for the individuals with intellectual deficiency, their family and the involved services. Much research has been conducted on interventions in this area. Treatment strategies that are frequently employed are pharmaceutical and psychotherapeutic interventions, sometimes supplemented with contextual strategies.

Preoperative Preparation

Lack of cooperation of a child with behavioral problem can be predictable; therefore
one important principle is that the surgeon notifies in advance the anesthesiologist about the scheduling of such child for a procedure requiring anesthesia. Multidisciplinary discussions about the indications, urgency and timing of interventions requiring anesthesia may be of benefit\textsuperscript{18}. Once the anesthesiologist notified, he can contact the parents and the severity of the disability and behavior of the child can be determined. Various strategies may be discussed with them, whilst recruiting their help and support. In children with severe learning disabilities, a multidisciplinary team of support workers trained in communication and interaction with these children is often required to assist them in most aspects of daily living\textsuperscript{19}. Eighty percent of children with severe learning disabilities fail to acquire effective speech\textsuperscript{20}. Hence, these professional caregivers become an essential interface between the child and the hospital staff. They are able to communicate the child’s needs and interpret some of the behavior otherwise dismissed as being part of having a severe learning disability. Professional caregivers usually have a risk profile for each child documenting behavioral patterns, aggression, violence, sources of anxiety, likes and dislikes as well as a history of medical problems and current medications\textsuperscript{21}. Management options can be discussed by telephone, at a preoperative assessment clinic or at the routine preoperative visit and should be documented. A clear plan for types and routes of premedication, use of restraint, the choice of induction technique and recovery plans needs to be established. Consent is obtained from the legal guardian, which may be a parent or a representative of the social services.

To many children with behavioral problems, the disruption to their normal routine will be a source of great anxiety and may precipitate panic attacks or temper tantrums; therefore every effort should be made to explain as much as possible to the child in an appropriate way of communication. Interventions may include basic explanation or teaching, as well as behavioral management in more severe cases\textsuperscript{22}. A preoperative theater visit, mock inductions, rewards, and family counseling can be of great value. Postponement of the procedure may be appropriate to institute these measures. Children may benefit from behavioral management strategies with play therapists or clinical psychologists\textsuperscript{23}. Professional caregivers often have training in behavioral treatments and functional communication which are invaluable in the preparation of the child at hospital. Positive reinforcement techniques target a positive outcome if the desired behavior is obtained e.g. the reward is a drink after the operation. Negative reinforcement focuses on the removal of an undesirable outcome e.g. the pain will be gone. Extensive repetition of these outcomes is used prior to arriving at the hospital and has been shown to reduce challenging behavior. Functional communication allows the child to communicate without resorting to challenging behavior to express themselves\textsuperscript{24}.

Placing children with behavioral problems first on the operative list is important to minimize waiting or starvation periods and list delays. An early start also allows an early recovery and return home, if suitable. A room on the ward or day care unit should be identified where the child can wait and be assessed minimizing exposure to any stresses but also enabling the caregivers to maintain control easily. Autistic children respond very well to reducing amount of distressing sensory input such as noise, movement and light particularly in unfamiliar surroundings\textsuperscript{25}. Outpatients may be allowed to retain their normal clothing and all children are encouraged to bring personal comfort objects to the hospital. A child/family friendly ward, holding area, anesthetic room, operating theater and recovery area, with toys,
games and reading material for a range of ages can be of great help\textsuperscript{26}. Staff behavior can greatly affect the frequency and severity of challenging behavior\textsuperscript{27}. Hospital staff is usually not trained in communication skills and have been identified as lacking knowledge, training and confidence in managing challenging behavior. However, adequate communication may be easier to achieve in a dedicated pediatric unit.

**Premedication**

Nonpharmacological approaches applied to relieve child anxiety rarely work alone in children with maladaptive behavioral disorders and hence pharmacological approach is often required\textsuperscript{28}. In children with anticipated difficult behavior such as autistic children, noncompliance at induction increased from 22\% to 50\% when a premedicant was not given\textsuperscript{29}. There is a wide variation in premedication requirements depending on the severity of the child’s behavior. Careful assessment, based on the individual anesthetist’s assessment is therefore needed to judge about the drug and its route of administration.

Premedication modifies behavior by providing amnesia, anxiolysis and sedation. However, there are advantages and disadvantages to amnesia. Any beneficial adaptive behavioral changes gained are not recalled but it may also prevent increasingly maladaptive behavior developing. Sedation may be the most likely behavior change to improve compliance at induction\textsuperscript{30}. Premedication should be both acceptable and effective. The oral route is the route of choice. However, not all current formulations are pleasant to taste. Acceptance may require coercion by a trusted companion, disguise in a drink and ingestion in an unthreatening environment, perhaps even offsite. Occasionally, where ‘more demanding’ challenging behavior has been identified, premedication is required at home prior to arrival at the hospital in order to minimize violent or self-injuring behavior. Benzodiazepines are clearly established as effective premedicant. Midazolam is the most commonly used benzodiazepine for premedication\textsuperscript{31}. The recommended optimal oral dosage for midazolam is 0.25-1 mg/kg. The most common used dose is 0.5 mg/kg. Clinical sedative effects of oral midazolam are seen within 10 min and the peak effect is achieved in 20-30 min. Finley et al. showed that midazolam-induced decrease in anxiety was more pronounced for children with higher baseline levels of anxiety. They concluded that midazolam was contraindicated in children with high trait impulsivity and beneficial only if the child has a high state anxiety level at baseline\textsuperscript{32}. Oral ketamine is a popular alternative to oral benzodiazepines. Ketamine is not associated with respiratory depression, tachycardia or emergence agitation. A large dose of oral ketamine (3-8 mg/kg) can be well tolerated. In autistic children with behavior disorders, compliance at induction was improved by adding ketamine compared with midazolam alone without any increase in unwanted side-effects\textsuperscript{29}. The combination of midazolam and ketamine at lower doses may be used in the extremely uncooperative child\textsuperscript{33}. Clonidine is an \( \alpha_2 \)-adrenergic agonist that has been used as an oral sedative premedication in children. In doses of 2-4 \( \mu \)g/kg, oral clonidine will produce adequate sedation and anxiolysis. Mehta et al. reported successful use of oral clonidine for sedation of autism and pervasive developmental disorders\textsuperscript{34}. Dexmedetomidine is a more selective \( \alpha_2 \)-adrenergic agonist and is
also being used as premedicant in children in oral and intranasal routes. Zub used oral dexmedetomidine at the dose of 1-4 μg/kg and found it effective even in patients with neurobehavioral disorders in whom previous attempts at sedation had failed\textsuperscript{35}. When compared to oral midazolam, intranasal dexmedetomidine at a dose of 2.5 μg/kg produces more sedation, but with similar and acceptable cooperation\textsuperscript{36}. However, α₂-adrenergic agonists do not have an amnestic effect. The decision about the use of midazolam or α₂-adrenergic agonist will depend on the long-term effects on the implicit and explicit memory of children. Occasionally the oral route may not be possible and alternatives routes should be considered such as intranasal, intramuscular, subcutaneous, rectal and transmucosal (lollipop) routes. However, none of these appear very suitable for a child with severe behavioral problems. Although the aim is to avoid the intramuscular route as much as possible in children, instead of struggling with a combative child for a long time, performing a very brief intramuscular injection may be advised. An intramuscular dose of Ketamine 4-5 mg/kg provides effective sedation in 93-100% of children in 5 min and the duration of action is approximately 45 min\textsuperscript{37}.

Premedication must be given in a quiet area with minimal distractions. Following premedication, the child should be observed. Before separation from the parent or intravenous access, enough time should be allowed to achieve onset time of premedicant. Once the onset of sedation has occurred, this may allow the application of local anesthetic cream to the hands of the child. Assessment by the anesthetist at regular intervals allows the child to be introduced onto the list at an appropriate time to coincide with the optimal depth of sedation. In such children, there should be no excuse for delays or rush.

**The Anesthetic Room**

The anesthetic room is used to reinforce calming strategies used so far. Parental presence during induction has been shown to effectively reduce preoperative anxiety in children in certain contexts; when the parent is calm and the child is anxious\textsuperscript{38}. However, it’s advisable that children with learning disability be accompanied by the primary caregiver who can provide reassurance and interpret any communication or behavioral changes. Low sensory environments such as low lighting and soft music have been shown to reduce anxiety scores on entering the anesthetic room and on induction of anesthesia in children. Various techniques of distraction appropriate for the level of development of the child may be used including music, television, toys or hypnotherapy\textsuperscript{39}. Some children violently resist interventions or procedures after careful preparation. These are a challenging group of patients, who risk damage to themselves, and stress to their families and staff. The anesthetist must rapidly decide between postponement or physical restraint. Numerous guidelines exist detailing the correct approaches, techniques and legal aspects of restraint in children\textsuperscript{40}. All of these guidelines emphasize that whilst an appropriate level of restraint may be necessary in some situations, the potential hazards such as physical or psychological harm, loss of dignity, and violation of human rights must be recognized and alternative strategies sought wherever possible. In spite of the documented disadvantages, the use of restraint during induction of
anesthesia can be justified as a last resort with parental and staff consent, provided the conditions are appropriate and the indications sufficient. Restraint, once started, must be decisively, speedily and effectively applied by a sufficient number of staff and continued until induction is completed. Restraint techniques should be performed by staff after individualized instructions and not left to a terrified parent. Skilled technique minimizes the risk of harm to child and staff\textsuperscript{41}. Both types of induction of anesthesia, inhalation or intravenous can be safe, and their success depends upon the regular practice of appropriate methods and protocols.

Emergence agitation may be more common during recovery in children with prior behavioral problems. Tait demonstrated that, compared to children without attention deficit, hyperactivity disorder (ADHD), children with ADHD exhibited an increase in maladaptive behaviors postoperatively\textsuperscript{42}. To decrease the incidence of emergence agitation, a number of pharmacologic and non-pharmacologic approaches have been recommended. Some authors recommended the avoidance of low solubility inhalational anesthetic, the preoperative and intraoperative administration of clonidine or dexmedetomidine\textsuperscript{43}, as well as the use of propofol as total intravenous anesthesia or as single injection before the end of surgery\textsuperscript{44,45}. Involving the parents early in the recovery phase and removal of i.v. drips and cannulae is important. The administration of i.v. fluids and antiemetics to allow early removal of the i.v. cannula before the child becomes distressed by its presence should be routinely done. Analgesia must be carefully managed as children with learning difficulties may have difficulty in expressing the location and intensity of pain postoperatively. Simple analgesics should be used routinely and supplemented by a local anesthetic technique if appropriate.

Consideration must also be given to the place of recovery. It is important to realize that children with behavioral problems react badly to any change in their routine and therefore waking up in strange surroundings can be very alarming for them. Management as ambulatory cases with early discharge is also aimed for in order to return patients to their normal environment at the earliest opportunity. If they need overnight admission, the provision of a side room in the ward to minimize exposure to other people might be beneficial.

Children with behavioral disorders are a varied group ranging from normal to children with severe intellectual deficiency. Children with disability and their parents often feel undervalued and stigmatized. Health care professionals need to reflect on their own attitudes and values to ensure that the care delivered is of an equally high standard to that normally provided to children without disability. Awareness and understanding of their special requirements is essential when devising a management plan. Advanced planning, flexible admission system, communication between surgeons, anesthetists, nurses, parents, caregivers and most importantly the child is vital to ensure that the visit to the operating room is as smooth and stress-free as possible.
References


THE PREGNANT PATIENT WITH PULMONARY ARTERY HYPERTENSION

- A Review -

ELIZABETH A.M. FROST*

Introduction

The first international conference on pulmonary hypertension was organized by the World Health Organization in 1973. At that time there were no effective therapies and patients with primary or idiopathic pulmonary hypertension had a median survival of less than 3 years. Now many treatments have more than doubled the survival time and more patients present for surgery and anesthesia and survive to become pregnant. Nevertheless, pregnancy complicated by pulmonary hypertension poses risks to the mother that can prove fatal. Two recent articles have outlined the current treatment modalities and the management of pulmonary hypertension during pregnancy1,2.

Classification of Pulmonary Hypertension

Pulmonary hypertension (PH) is an increase in pressure in the pulmonary artery, vein or capillaries (lung vasculature), leading to dyspnea, dizziness, fainting, and other symptoms, all of which are exacerbated by exertion. Pulmonary hypertension can be a severe disease with a markedly decreased exercise tolerance and heart failure. First identified by Dr. Ernst von Romberg in 18913, pulmonary hypertension was previously divided into 2 categories: primary pulmonary hypertension and secondary pulmonary hypertension, based on identifiable etiology. In 1998, the World Health Organization (WHO) proposed a clinical classification of pulmonary hypertension based on similarities in pathophysiology, clinical presentation, and therapeutic options, classifying PH to one of five different types4: arterial, venous, hypoxic, thromboembolic or miscellaneous.

As noted above, the 1973 meeting organized by the World Health Organization was the first to attempt classification of pulmonary hypertension. A distinction was made between primary and secondary PH, and primary PH was divided to the "arterial plexiform", "veno-occlusive" and "thromboembolic" forms. A second conference in 1998 at Évian-les-Bains also addressed the causes of secondary PH (i.e. those due to other medical conditions), and in 2003, the 3rd World Symposium on Pulmonary Arterial Hypertension was convened in Venice to modify the classification based on new understandings of disease mechanisms. The revised system developed by this group provides the current framework for understanding pulmonary hypertension. The system includes several improvements over the former 1998 Evian Classification system. Risk factor descriptions were updated, and the classification of congenital systemic-to pulmonary shunts was revised. A new classification of genetic factors in PH was recommended, but not implemented because available data were judged to be inadequate4.

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The Venice 2003 Revised Classification system can be summarized as follows:

- **Group I - Pulmonary arterial hypertension (PAH)**
  - Idiopathic (IPAH)
  - Familial (FPAH)
  - Associated with other diseases (APAH): collagen vascular disease (e.g. scleroderma), congenital shunts between the systemic and pulmonary circulation, portal hypertension, HIV infection, drugs, toxins, or other diseases or disorders
  - Associated with venous or capillary disease

- **Group II - Pulmonary hypertension associated with left heart disease**
  - Atrial or ventricular disease
  - Valvular disease (e.g. mitral stenosis)

- **Group III - Pulmonary hypertension associated with lung diseases and/or hypoxemia**
  - Chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD)
  - Sleep-disordered breathing, alveolar hypoventilation
  - Chronic exposure to high altitude
  - Developmental lung abnormalities

- **Group IV - Pulmonary hypertension due to chronic thrombotic and/or embolic disease**
  - Pulmonary embolism in the proximal or distal pulmonary arteries
  - Embolization of other matter, such as tumor cells or parasites

- **Group V Miscellaneous. Pulmonary hypertension due the direct effect on the pulmonary vasculature of inflammatory diseases such as schistosomiasis, sarcoidosis, histocytosis X, and fibrosing mediastinitis.**

  The classification does not include sickle cell disease, which may also cause PH. Also, Human herpes virus 8, also associated with Kaposi’s sarcoma, has been demonstrated in patients with PAH, suggesting that this virus may play a role in its development. An association between human herpesvirus 8 and idiopathic pulmonary arterial hypertension (IPAT) remains controversial.

**Pathogenesis**

Whatever the initial cause, pulmonary arterial hypertension (WHO Group I) involves the vasoconstriction of blood vessels connected to and within the lungs increasing cardiac load. Over time, the affected blood vessels fibrose, further increasing pressure within the lungs and impairing blood flow. The right ventricular hypertrophies (cor pulmonale develops), decreasing the ability of the heart to pump blood through the lungs, ultimately causing right heart failure. As blood flow through the lungs decreases, the left side of the heart receives not only less blood but also poorly oxygenated blood, decreasing the ability to supply sufficient oxygen to the rest of the body, especially during physical activity.

Pathogenesis in pulmonary venous hypertension (WHO Group II) differs in that, there is no obstruction to
blood flow in the lungs. Instead, the left heart fails to pump blood efficiently, leading to pooling of blood in the lungs causing pulmonary edema and pleural effusions.

In hypoxic pulmonary hypertension (WHO Group III), the low levels of oxygen are thought to cause vasoconstriction of pulmonary arteries leading to a pathophysiology similar to pulmonary arterial hypertension.

In chronic thromboembolic pulmonary hypertension (WHO Group IV), vessels are blocked or narrowed with blood clots. Again, the pathology is similar to that seen in pulmonary arterial hypertension.

A further classification is made on functional ability. These classes are based on information adapted from the executive summary of the world symposium on Primary Pulmonary Hypertension in Evian, France in 1998.

- **Class I:** These are patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
- **Class II:** These are patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
- **Class III:** These are patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
- **Class IV:** These are patients with pulmonary hypertension with an inability to perform any physical activity without symptoms. These patients manifest signs of right-sided heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

### Epidemiology

The overall prevalence of pulmonary hypertension in the general population is unknown, owing to the heterogeneity of the disease. In specific subgroups of pulmonary hypertension patients, studies have estimated the prevalence as follows:

- In an observational study of 277 patients with HIV infection, 46% of patients had pulmonary hypertension. In comparison with prior studies, no change in prevalence rate was seen with modern highly active antiretroviral treatment (HAART)

- A systematic review of several studies of patients with obstructive sleep apnea (OSA) estimated the prevalence of pulmonary hypertension at 15-20%.

- A systematic review of several studies among patients with chronic obstructive pulmonary disease (COPD) estimated the prevalence of pulmonary hypertension at 10-30%.

- In scleroderma patients, the incidence has been estimated to be 6-60% of all patients, with the variance based on the extent of disease.

- In patients who took the diet medication fenfluramina/phentermine, there was a 23x increase in the development of PH, often long after ingestion of the drug combination.

Regarding mortality and morbidity for patients with PH and based on the US Centers for Disease Control and Prevention (CDC) Pulmonary Hypertension Surveillance from 1980-2002, the following were reported:

- The age-standardized death rates for the total US population increased from 5.2 deaths to 5.4 deaths per
The main increase in death rates was seen among women, with 3.3 deaths to 5.5 deaths per 100,000 population, and blacks, with 4.6 deaths to 7.3 deaths per 100,000 population.

The death rate in males decreased over this time, from 8.2 deaths to 5.4 deaths per 100,000 population.

**Diagnosis**

Because of the many etiologies of PH a series of tests must be performed to distinguish pulmonary arterial hypertension from venous, hypoxic, thromboembolic, or miscellaneous varieties.

A physical examination looks for typical signs of pulmonary hypertension including altered heart sounds, such as a widely split $S_2$ or second heart sound, a loud $P_2$ or pulmonic valve closure sound (part of the second heart sound), (para)sternal heave, possible $S_3$ or third heart sound, and pulmonary regurgitation. Other signs include an elevated jugular venous pressure, peripheral edema, ascites, hepatojugular reflux, and clubbing.

Further procedures are required to confirm the presence of pulmonary hypertension and exclude other possible diagnoses. These generally include pulmonary function tests; blood tests to exclude HIV, autoimmune diseases, and liver disease; electrocardiography (ECG); arterial blood gas measurements; X-rays of the chest (followed by high-resolution CT scanning if interstitial lung disease is suspected); and ventilation-perfusion or V/Q scanning to exclude chronic thromboembolic pulmonary hypertension. Thoracic echocardiography (TTE) is used widely as a screening tool for PH. There is good correlation between PA pressures and right ventricular systolic pressure. However, several factors such as severe lung disease, premature ventricular contractions, and inaccurate estimates of right atrial pressure can lead to misdiagnosis. Studies have found that TTE may overestimate PA pressures when compared with right heart catheterization (RHC)\(^2\). On the other hand, in about one third of patients, RHC may reveal more severe PH than is estimated from TTE. Thus both under and over estimating may occur. However, PH does not mean PAH is present and thus assessment of PA occlusion pressures and PVR must be made. In fact, the diagnosis of PAH must be made confirmed with RHC in pregnant patients, given the high morbidity and mortality associated with the combination of the two conditions. Biopsy of the lung is usually not indicated unless the pulmonary hypertension is thought to be due to an underlying interstitial lung disease. Lung biopsies carry risks of bleeding due to the high intrapulmonary blood pressure. Clinical improvement is often measured by a "six-minute walk test", i.e. the distance a patient can walk in six minutes. Stability and improvement in this measurement correlate with better survival. Brain natriuretic peptide levels (BNP) may be used to follow the progress of patients with pulmonary hypertension.

Although pulmonary arterial pressure can be estimated on the basis of echocardiography, pressure measurements with a pulmonary artery (PA) catheter provides the best assessment. PAOP and PVR cannot be measured directly by echocardiography. Therefore diagnosis of PAH requires right-sided cardiac catheterization. A PA catheter can also measure cardiac output, which is more important in measuring disease severity than pulmonary arterial pressure. Diagnosis of PAH requires the presence of pulmonary hypertension with two other conditions. Pulmonary artery occlusion pressure (PAOP or PCWP) must be less than 15 mm Hg (2000 Pa) and pulmonary vascular resistance (PVR) must be greater than 3 Wood units (240 dyn•s•cm\(^{-5}\) or 2.4 mN•s•cm\(^{-5}\)). Normal pulmonary arterial pressure in a person at sea level has a mean value of 12–16 mmHg (1600-2100 Pa). Pulmonary hypertension is present when mean pulmonary artery pressure exceeds 25 mmHg (3300 Pa) at rest or 30 mmHg (4000 Pa) with exercise. Mean pulmonary artery pressure (mPAP) should not be
confused with systolic pulmonary artery pressure (sPAP), which is often reported on echocardiogram reports. A systolic pressure of 40 mm Hg typically implies a mean pressure of more than 25 mmHg. Roughly, mPAP = 0.61•sPAP + 2.

**Physiologic Changes of Pregnancy**

There are several cardiopulmonary physiologic changes with pregnancy that exacerbate PH. In the pulmonary system, minute ventilation increases by 50% at term. Arterial carbon dioxide decreases to about 34mmhg. Functional residual capacity, expiratory reserve volume and residual volume all decrease. Total lung capacity remains the same because of increase in chest circumference. The smooth muscle relaxation effects of progesterone may decrease airway resistance and improve function. Cardiac changes include a 50% increase in cardiac output, with early increases in blood volume that lead to increased stroke volume. Afterload is reduced secondary to decreased peripheral vascular resistance. Later, cardiac output is augmented by tachycardia. Normally, pulmonary vascular resistance (PVR) decreases to allow for these changes, an accommodation that is not possible in patients with PH. As afterload increases from the higher PVR, the right ventricle cannot handle the increased cardiac output and begins to fail. Sudden death from dysrhythmia may occur. Peak plasma volumes develop about 22-24 weeks and cardiac output peaks around 32 weeks.

At the time of delivery, pain stimulates the sympathetic nervous system with sudden significant increases in heart rate, blood pressure and myocardial oxygen consumption. Vagal responses may also occur and lead to hypotension and sudden death. Valsalva maneuvers may further increase blood pressure and myocardial oxygen consumption. Also, with each uterine contraction, about 500ml blood is pushed into the maternal circulation. After delivery, autotransfusion from the uterine circulation and increased venous return from the relief of inferior vena cave pressure cause large fluid shifts to the maternal circulation. Right ventricular volume overload can occur easily.

Pregnancy is associated with a hypercoagulable state due to increased fibrin levels, reduced fibrinolytic activity, increased procoagulant activity with higher resistance to activated protein C, lower protein S, and increased clotting factor activity. Any degree of thromboembolism contributes to a poor outcome in pregnant patients with PH.

**Pulmonary Hypertension and Pregnancy**

Pulmonary hypertension affects a relatively small number of pregnancies (approximately 0.0003%). However, mortality is reported as high as 60% in older studies. More recent studies indicate a decline in mortality to around 25%, with patients in the IPAH group showing the most improvement (17%), perhaps due to the incorporation of PAH specific therapy which is more likely to be used for patients with IPAH.

Previously undiagnosed PH may manifest first with the stress of pregnancy. It can also develop acutely during pregnancy. Sudden onset of dyspnea, syncope or chest pain should be immediately investigated. Differential diagnosis includes: sleep apnea, asthma, arteriovenous malformations, atrial myxoma, amniotic fluid embolism, atrial septal defect, cardiomyopathy (dilated, hypertrophic or restrictive), chronic obstructive pulmonary disease, emphysema, mitral regurgitation and stenosis, restrictive and interstitial lung disease and systemic lupus erythematosus.
As soon as a diagnosis of PH is made, patients should be followed with regular assessment of RV function with TTE. Should dysfunction be detected, early delivery is recommended\(^2\). While no anesthetic technique has proven superior, most patients were delivered in the few studies reported under spinal or epidural anesthesia\(^2\). Of note is that during delivery, hypotension may develop from the several medications used to treat PH including oxytocin, pulmonary vasodilator drugs, inotropes (dobutamine) and analgetics. Vasopressin preferentially increases systemic vascular resistance without increasing PVR and is a viable option to support blood pressure without compromising RV function. Maternal death is most likely to occur in the postpartum period when maximum fluid shifts occur.

**Treatment**

While there is no curative therapy short of lung transplantation, several treatments have shown promise in improving outcome for patients with PH. Therapy is dictated in part by the cause, whether it be arterial, venous, hypoxic, thromboembolic, or other. Since pulmonary venous hypertension is synonymous with congestive heart failure, the treatment is to optimize left ventricular function by the use of diuretics, beta blockers, ACE inhibitors, etc., or to repair/replace the mitral valve or aortic valve. Digoxin, diuretics, and oxygen have been advocated but results are inconsistent. High dose calcium channel blockers are useful in only 5% of IPAH patients who are vasoreactive by pulmonary artery catheter measurements. Unfortunately, calcium channel blockers have been largely misused, being prescribed to many patients with non-vasoreactive PAH, leading to excess morbidity and mortality. The criteria for vasoreactivity have changed. Only those patients whose mean pulmonary artery pressure falls by more than 10 mm Hg to less than 40 mmHg with an unchanged or increased cardiac output when challenged with adenosine, epoprostenol, or nitric oxide are considered vasoreactive.\(^15\) Of these, only half are responsive to calcium channel blockers in the long term\(^16\). Several agents have recently been introduced for primary and secondary PAH. The trials supporting the use of these agents have been relatively small, and the only measure consistently used to compare their effectiveness is the "6 minute walking test". Many have no data on mortality, benefit or time to progression\(^17\).

RV failure is the most common cause of death in pregnant patients with PH. Thus therapy has aimed at reducing PVR. Three of the many vasoactive pathways involved in the abnormal proliferation and contraction of the smooth muscle cells of the pulmonary arteries have been targeted with drugs - endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclin derivatives. Prostacyclin (prostaglandin I\(_2\)) is commonly considered the most effective treatment for PAH. Epoprostenol (synthetic prostacyclin, marketed as Flolan) is given via continuous infusion that requires a semi-permanent central venous catheter. This delivery system can cause sepsis and thrombosis. Flolan\(^\circledast\) is unstable, and therefore has to be kept cold during administration. Since it has a half-life of 3 to 5 minutes, the infusion has to be continuous (24/7), and interruption can be fatal. Other prostanoids have therefore been developed. Treprostinil (Remodulin\(^\circledast\)) can be given intravenously or subcutaneously, but the subcutaneous injection can be very painful. An increased risk of sepsis with intravenous Remodulin has been reported by the CDC. Iloprost (Ilomedin\(^\circledast\)) is also used in Europe intravenously and has a longer half life. Iloprost (marketed as Ventavis\(^\circledast\)) was the only inhaled form of prostacyclin approved for use in the US and Europe, until the inhaled form of treprostinil was approved by the FDA in July 2009 and is marketed under the trade name Tyvaso\(^\circledast\). The inhaled form of administration has the advantage of selective deposition in the lungs with less systemic side effects, however coughing and throat irritation commonly occur. Oral and inhaled forms of Remodulin\(^\circledast\) are under development. Beraprost is an oral
prostanoid available in South Korea and Japan.

The dual (ET\textsubscript{A} and ET\textsubscript{B}) endothelin receptor antagonist bosentan (marketed as Tracleer\textsuperscript{®}) was approved in 2001. Sitaxentan, a selective endothelin receptor antagonist that blocks only the action of ET\textsubscript{A}, has been approved for use in Canada, Australia, and the European Union, marketed under the name Thelin\textsuperscript{®}. It has not been approved for marketing by the U.S. Food and Drug Administration (FDA). In 2010, Thelin\textsuperscript{®} was withdrawn by Pfizer due to severe side effects. A new trial to address the FDA’s concerns began in 2008. A similar drug, ambrisentan is marketed as Letairis\textsuperscript{®} in U.S. (Gilead Sciences). In addition, another dual/nonselective endothelin antagonist, Actelion-1, from the makers of Tracleer\textsuperscript{®}, entered clinical trials in 2008.

Sildenafil, a selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5), was approved for the treatment of PAH in 2005, marketed as Revatio\textsuperscript{®}. In 2009, tadalafil, another PDE5 inhibitor, marketed under the name Adcirca\textsuperscript{®} or Cialis\textsuperscript{®} was also approved.

The nitric oxide (NO) signaling pathway is important for many physiological functions including vascular smooth muscle relaxation, neuronal signal transduction and inhibition of platelet aggregation. The source of NO in vivo is the enzyme nitric oxide synthase. The principal receptor for NO is soluble guanylate cyclase (sGC). Several sGC activators including cinaciguat and riociguat are undergoing clinical trials for the treatment of PAH.

There is conflicting data as to the fetal effects of these medications. However, at least anecdotal reports indicate safe usage with most of them\textsuperscript{2}.

Several surgical procedures have been described for the treatment of PH. Atrial septostomy creates a communication between the right and left atria and relieves pressure on the right side of the heart, but at the cost of relative hypoxia. Lung transplantation cures pulmonary arterial hypertension, but leaves the patient with the complications of transplantation, and a post-surgical median survival of just over five years\textsuperscript{18}. Pulmonary thromboendarterectomy (PTE) is a difficult, major procedure that is currently performed in a few select centers but with apparent good success in select patients.

**Management of a Typical Case**

A 39 year old woman, approximately 18 weeks pregnant presented to the emergency room complaining of excessive tiredness, dyspnea, syncope and ankle swelling. She had never had surgery and this was her first pregnancy. To date she had had no prenatal care. She reported taking several mutivitamin preparations and some herbals. Several years before she was told that she had a heart murmur. On physical examination she weighed 215lbs and was 64in tall. There was slight cyanosis of her lips and marked swelling of her feet and ankles. On auscultation, split S2 and loud P2 sounds were heard. BP 155/95, Heart rate 101 with frequent PVC’s, spO\textsubscript{2} 92 on room air. Hct 29%, blood sugar, 189mg/dl.

A diagnosis of pulmonary artery hypertension was made and she was tentatively scheduled for termination of pregnancy. Anesthetic consultation was sought.

Right heart catheterization indicated that the patient had severe pulmonary hypertension (WHO Group IV). Further evaluation determined that she had sarcoidosis. She was counseled as to continuation of the pregnancy. Given her obesity and gestational diabetes and the established right heart dysfunction it was agreed that late termination would be the safer choice with steroid therapy for the treatment of sarcoid. The patient was
reluctant to agree as this was her first and perhaps only pregnancy. She was given further opportunity to discuss the situation and to review the available data with a team of obstetricians, cardiologists, pulmonologists and anesthesiologists with input from psychologists and social workers. She acknowledged that the chances of her survival and that of the baby were less than 50% and she agreed to proceed with termination. A course of prednisone and high dose calcium channel blockers was started.

Decision was made to perform the termination in an operating room prepared for open heart surgery. A cardiac surgeon was placed on stand by as was the entire team. Anxiolysis was achieved with midazolam 4mg. The radial artery was cannulated and a pulmonary artery catheter placed. After antacid prophylaxis, caudal analgesia was achieved. Vasopressin was prepared but was not required. Evacuation was completed in 12 minutes. Oxytocin was withheld because of the theoretical risk of increase of PVR. The patient was transferred to the ICU and carefully observed for 24 hours. She was then discharged for further evaluation prior to mitral valve replacement.

**Conclusion**

Pulmonary hypertension complicating pregnancy carries serious considerations for anesthetic management. As the pregnancy progresses, the risk of sudden death increases. Diagnosis as to the cause of the pulmonary hypertension is essential. Close communication with cardiology, pulmonology and obstetrical teams are essential. Psychological support for the patient is also indicated as termination is frequently the safer route for the mother.
References

PREECLAMPSIA, A NEW PERSPECTIVE IN 2011

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I-Introduction-Definitions

Preeclampsia is one of the most commonly encountered hypertensive disorders of pregnancy (HDP). It is mostly feared because of its serious maternal and fetal mortalities and morbidities. Ten percent of women have high blood pressure (BP) during pregnancy, and preeclampsia complicates 2% to 8% of pregnancies. Overall, 10% to 15% of direct maternal deaths are associated with preeclampsia and eclampsia. Worldwide, HDP accounts for more than 50,000 maternal deaths per year according to the world health organization (WHO). In fact, perinatal mortality is high following preeclampsia, and even higher following eclampsia.

The diagnosis of hypertension in pregnancy is reached when two BP readings show a systolic blood pressure (SBP) of ≥140 mmHg and/or a diastolic blood pressure (DBP) of ≥90 mmHg, taken over a period of 4 to 6 hours after 20 weeks gestation, in previously normotensive women. The American College of Obstetricians and Gynecologists (ACOG) developed a classification system for HDP in 2000. Accordingly, preeclampsia is defined by a constellation of findings present in a pregnant women including hypertension, proteinuria and/or organ dysfunction after 20 weeks of gestation. HELLP syndrome is a form of severe preeclampsia characterized by hemolysis, elevated liver enzymes, and low platelet count. Chronic hypertension is usually not related to pregnancy and presents before 20 weeks gestation. Moreover, there is a category of patients who present with preeclampsia on top of chronic hypertension. It is manifested by having a new onset of thrombocytopenia or proteinuria in a patient known to have chronic hypertension. Transient or gestational hypertension refers to the presence of hypertension in late pregnancy, without evidence of preeclampsia, and it resolves in the postpartum period.

Proteinuria in preeclampsia is considered pathological when patients present with a total of 300 mg in 24 hours. Usually screening for proteinuria is done with urine dipstick. If a dipstick results in more than or equal 1+ of protein, a 24 hour collection should be ordered since the sensitivity of dipstick testing for proteinuria is only 61%, with a specificity of 97%. The role of the protein:creatinine ratio is still controversial, thus the 24 hours urine collection is the gold standard of investigation.

Preeclampsia may progress from mild to severe when the SBP becomes more than 160 mmHg or DBP more than 110 mmHg, proteinuria more than 5g per 24 hours or any sign of end organ damage. However, preeclampsia can be diagnosed in special situations in the absence of proteinuria. A significant deterioration of renal function with elevation of serum creatinine to levels greater than 0.9 g/L or oliguria <500mL/day, severe epigastric pain along with elevated liver enzymes level indicating liver involvement with overstretching of the hepatic capsule, pulmonary edema manifested by dyspnea and oxygen desaturation, thrombocytopenia, hemolysis, disseminated intravascular coagulation (DIC), severe headache, persistent visual disturbance,
hyperreflexia or intrauterine growth restriction (IUGR) reflect the most common systemic dysfunctions of severe preeclampsia. When tonic-clonic seizures occur along with preexisting signs of preeclampsia, the diagnosis of eclampsia is reached (0.03% to 0.1% of all pregnancies).

The severity of proteinuria does not correlate with maternal morbidity and it should not be considered an indication for delivery. There is still no evidence to support the 300 mg/24 hours cutoff used to diagnose preeclampsia; nor agreement about the degree of proteinuria that should be considered severe since protein clearance is altered during pregnancy. Consequently, the management decisions should not be based on the degree of proteinuria rather on other clinical indicators of the severity of the disease, such as BP, liver dysfunction, or deteriorating neurologic status.

The spectrum of this disease should remit by 6-12 weeks postpartum. Such overwhelming morbidities created a need for a new appraisal of the literature, with the goal of finding ways of early diagnosis and a comprehensive management.

II-Etiology-Pathophysiology

Many theories were proposed to understand the exact mechanism causing the multiple pathologic changes observed in preeclampsia. It is a multisystem disease in nature. The theory of early onset preeclampsia being of placental origin was introduced due to abnormal remodeling of spiral arteries. Cytotrophoblastic cells infiltrate the decidual portion of the spiral arteries, but do not penetrate the myometrial segment. Spiral arteries fail to develop into large, tortuous vascular channels resulting in placental hypoperfusion. The impaired placentation and resultant ischemia are thought to be the primary events leading to placental release of soluble factors that cause systemic endothelial dysfunction. Late placental changes consistent with ischemia include atherosis, fibrinoid necrosis, thrombosis, sclerotic narrowing of arterioles, and placental infarction.

The second theory is of immunologic origin. It is thought that certain abnormalities similar to organ rejection graft versus host occur. The extravillous trophoblast cells express a combination of HLA class I antigens including HLA-C, HLA-E, and HLA-G. Natural killer cells infiltrate the maternal decidua with increased NK cell activity. Biopsies of different placentas from women with preeclampsia showed increased dendritic cell infiltration in decidual tissues. The increased number of dendritic cells may result in a change in presentation of maternal and fetal antigens at the decidual level, leading to abnormal implantation and altered maternal immunologic response to fetal antigens. Moreover, there is increased sensitivity to angiotensin II which may be related to increased bradykinin (B2) receptor upregulation leading to heterodimerization of B2 receptors with angiotensin II type I receptors.

Finally, the genetic theory of preeclampsia is suggested due to various observations. First, primigravid women with a family history of preeclampsia have a two- to five-fold higher risk of the disease. Also, the spouses of men who were the product of a pregnancy complicated by preeclampsia are more likely to develop preeclampsia. Lastly, a woman who becomes pregnant by a man whose previous partner had preeclampsia is at higher risk of developing the disorder than if the pregnancy with the previous partner was normotensive. Several genes including the angiotensinogen gene variant (T235), endothelial nitric oxide synthase (eNOS), and genes causing thrombophilia, have been proposed with preeclampsia.

III-Risk Factors of Preeclampsia
The most important risk factor of preeclampsia is the presence of previous history of a HDP. Other factors include body mass index >30 kg/m², pre-existing diabetes, renal disease, chronic hypertension, advanced maternal age >40 years, and family history. The relevance of inherited thrombophilia in the development of preeclampsia is still unclear, and there is no place for routine antenatal thrombophilia screening⁹. Patients with a previous history of severe or recurrent preeclampsia, HELLP syndrome, less than 34 weeks gestation, or IUGR should determine their level of anti-phospholipid antibodies¹³. The risk of recurrence of preeclampsia and especially HELLP syndrome should not be underestimated. In an early cohort study by Mostello et al., the absolute risk of recurrence of preeclampsia was 14.7%¹⁴. Recurrence of HELLP syndrome is between 2.1% and 19.1⁵. Early identification of women at high risk has been the subject of much research. Ideally, this would lead to timely interventions in order to minimize the risks of complications.

IV-Prediction of Preeclampsia

There is no reliable test for predicting preeclampsia in pregnancy; however, the use of uterine artery Doppler ultrasonography (U/S) is becoming more popular. If abnormal uterine flow manifested by a bilateral notch or high resistance index is present between 22 and 24th week gestation, there is a 60% risk of developing preeclampsia and/or IUGR later in pregnancy. The predictive value of Doppler U/S is particularly high for the development of severe preeclampsia before 34 weeks and for preeclampsia with IUGR¹⁶. Increased pulsatility index with notching after the 16th week of gestation is considered to be the best predictor of preeclampsia in women with risk factors¹⁷. The importance of combining maternal risk factors, early biochemical markers along with Doppler results from the first and second trimester is still being investigated. Certain anti-angiogenic proteins can be used to predict the occurrence of preeclampsia. Recently, a key role for soluble Flt1 protein and soluble endoglin was raised. These proteins are secreted by the placenta. There is a definite increase in the levels of Flt1 and endoglin proteins in the maternal circulation weeks before the onset of preeclampsia producing systemic endothelial dysfunction like hypertension, proteinuria¹⁸. New studies combined uterine Doppler with PlGF, sFlt-1 or sEng done during the second trimester and showed that early preeclampsia had a high detection rate ranging from 83 to 100% with a false positive of 11-24%¹⁹. Aquilina et al. found that inhibin A along with uterine Doppler had a detection rate of 43% with 3% false positive for early preeclampsia (<37 weeks)²⁰. Also, Spencer et al. found that second trimester uterine Doppler, PP13 and PAPP-A had a detection rate for early preeclampsia of 80% with 20% false positive. They also found that uterine Doppler, PP13 and β-hCG had a detection rate of 100% for early preeclampsia with 20% false positive²¹. Mice injected with auto-antibodies that activate the angiotensin II type 1a (AT1 receptor) resulted in a preeclampsia-like syndrome. Moreover, preeclampsia was prevented in the mice injected with Losartan, which is an AT1 receptor antagonist⁴.

V-Prevention of Preeclampsia

Studies suggest no reduction in the rate of preeclampsia with the use of oral magnesium, the antioxidant vitamins C and E, fish-oils, or oral calcium²². According to Hofmeyr et al., oral administration of calcium supplements at least 1g per day may significantly reduce the risk of preeclampsia in high risk patients with poor dietary calcium intake²³. Low dose oral aspirin, 75 to 150 mg per day, causes 17% reduction of the rate of preeclampsia compared to placebo, and 14% decrease in neonatal mortality when given before the 16th week of
It seems that the use of low dose aspirin inhibits the excessive production of thromboxane induced by preeclampsia without a significant effect on vascular prostacyclin production. Aspirin is not recommended if a pathological Doppler flow is present after 23 weeks. The use of prophylactic low-molecular weight heparin like dalteparin, weight adjusted, 4000-6000 IU/day, lowered the incidence of preeclampsia from 23.6% to 5.5% when used between 16 to 36 weeks of gestation.

VI-Obstetrical Considerations of Preeclampsia

The definitive treatment of preeclampsia is delivery of the baby. However, the gestational age plays an essential role in taking this decision. Patients are stratified according to the severity of their disease. Expectant management with bed rest until delivery along with frequent maternal monitoring and fetal surveillance is offered to women who are classified as having mild preeclampsia or gestational hypertension. Conservative management of mild preeclampsia is recommended because perinatal outcome is the same relative to normotensive pregnancies. If a woman is classified as having severe preeclampsia, then immediate admission to the delivery suite is recommended. Assessment of the patient is done in order to decide for delivery or medical treatment. First, the gestational age is determined. If the patient is still preterm, in other words, is less than 34 weeks of gestation, a trial of delaying delivery for promoting fetal lung maturity is considered. In this instance, delivery is delayed for 48 hours, and steroids are administered while the maternal BP is monitored and antihypertensive medications are used to keep SBP less than 160 and DBP less than 110 mmHg. The rationale for controlling maternal BP is to decrease the incidence of cerebral hemorrhage and preventing the occurrence of stroke and other maternal cerebrovascular complications. On the other hand, delivery of the patient is indicated if gestational age is less than 24 weeks, more than or equal 34 weeks, or in the presence of fetal or maternal distress manifested by eclampsia, DIC, renal failure, placental abruption, respiratory distress, or suspected liver hematomas.

In severe preeclampsia, therapy is directed towards controlling BP and to prevent the occurrence of eclampsia. Recently, studies were done to show the importance of systolic hypertension in patients with severe preeclampsia with respect to preventing stroke. Ninety three percent of the strokes reviewed were hemorrhagic and all patients had a SBP above 155 mmHg while only 12% had a DBP more than 110 mmHg. Moreover, extensive evaluation of the possible organs that might be affected is initiated starting with a complete blood count plus platelets, liver function tests, creatinine level plus electrolytes, urine analysis as well as 24 hour urine collection. Patients should be investigated for any neurologic symptom like headache or visual changes. They should also be asked about dyspnea because of the high incidence of pulmonary edema in this population. Fetal evaluation is done by doing a non-stress test, U/S and a biophysical profile. The placenta is visualized, growth restriction is determined and the exact gestational age is confirmed.

Antihypertensive drugs used for the management of preeclampsia include magnesium sulfate as a first line drug, hydralazine, labetalol, nitroglycerin, nitroprusside and calcium channel blockers like nifedipine and nimodipine. Magnesium sulfate is considered to be safe and effective in pregnancy. It dilates vascular beds by increasing prostacyclin and decreasing renin and angiotensin converting enzyme levels. Furthermore, it is used to prevent seizures and decrease the incidence of eclampsia. In fact, according to the Magpie Trial, women who were treated with magnesium sulphate had a 58% lower risk of eclampsia (95% CI 40-71) than placebo. Seizure prophylaxis is routinely accomplished with magnesium sulfate using a 4-6 g IV loading dose, then a 1-2 g/hour infusion, with a goal serum concentration of 5-8 mg/dL. The infusion should continue for at least 24
hours postpartum for prevention of eclampsia. However, there are multiple serious side effects of magnesium therapy that should not be overlooked. It depresses fetal heart rate variabilities, affects the neuromuscular functions of both the mother and the fetus, and can cause respiratory depression as well as cardiac toxicity. Thus, magnesium level is closely monitored to keep it at therapeutic levels. It is also reserved for patients with severe preeclampsia. In fact, women with mild preeclampsia don’t need magnesium sulfate therapy because 400 women with mild preeclampsia need to be treated to prevent one seizure according to the decision analytic model of magnesium therapy or no magnesium therapy. However, in severe preeclampsia the number needed to treat to prevent a seizure was 129 and 36 in severe preeclampsia with symptoms such as headache, visual disturbances or epigastric pain. Hydralazine 5-20 mg is also used in preeclampsia, but it crosses the placenta, causes reflex tachycardia and has unpredictable pharmacodynamics. Labetalol, an alpha and beta blocker, is useful because it does not cause reflex tachycardia and can be changed to an oral dose postpartum. As for nitroglycerin or nitroprusside, they are used in hypertensive emergencies like hypertensive encephalopathy since they have fast onset and short duration. Calcium channel blockers like nifedipine and nimodipine are also used in preeclampsia. They cause a fast drop in BP and improve urine output at the expense of causing uterine relaxation and postpartum atony. Of note, nifedipine has been safely used in conjunction with magnesium sulfate without significant evidence of increased serious magnesium-related side effects, such as muscle weakness.

VII-Anesthetic Considerations in Preeclampsia

The anesthetic management of a patient diagnosed with preeclampsia varies according to the decision of the mode and the timing of delivery. Preeclamptic patients may have a spontaneous vaginal delivery or may need a cesarean delivery. Neuraxial analgesia may be offered in cases where patients have normal platelet counts (more than 80,000-100,000/μL). Pre-anesthetic evaluation is critical. First, history and physical exam is done with special attention to the airway due to the increased risk of pharyngolaryngeal edema. Laboratory studies including urine protein, platelet counts, liver enzymes and possibly a coagulation panel are considered a prerequisite. Standard monitoring is initiated with an electrocardiogram, BP, and pulse oximetry. A Foley catheter is needed as well. In patients with uncontrolled hypertension invasive monitoring like an arterial line is required. Severely preeclamptic patients with pulmonary edema need a central venous line. Pulmonary artery catheter is used mainly in cases with severe cardiovascular disease, pulmonary hypertension and persistent oliguria. When the decision of cesarean delivery is taken, patients may be offered three anesthetic choices: spinal, combined spinal epidural, or general anesthesia (GA).

I-Neuraxial Anesthesia in Preeclampsia

The ACOG and the American Society of Anesthesiologists (ASA) recommend the use of regional anesthesia in preeclamptic patients without coagulopathy for both labor and delivery to avoid general anesthesia and to benefit from the advantages of neuraxial analgesia. Neuraxial anesthesia provides the best quality of analgesia, attenuates hypertensive responses to pain, reduces circulating catecholamines and does not require preloading with fluids when using dilute solutions. When choosing regional anesthesia, caution must be undertaken not to overload patients with fluids. Restriction of fluids at 80-100 ml/hour is needed in preeclamptic patients for minimizing the risk of pulmonary edema which often occurs in the postpartum period.
in patients with fluid overload or heart failure. As a matter of fact, pulmonary edema is associated with high perinatal mortality and morbidity.

Vasopressors such as phenylephrine and ephedrine should be used for the treatment of hypotension even if it is mild to maintain adequate uteroplacental perfusion. ASA recommend early insertion of a spinal or epidural catheter for obstetric or anesthetic indications to reduce the need for GA if an emergent procedure becomes necessary. In these cases, the insertion of a spinal or epidural catheter may precede the onset of labor or a patient’s request for labor analgesia. Many studies have been conducted in the last decade that emphasized the fact that spinal and combined spinal epidural anesthesia can be administered safely. Visalyaputra et al. in a prospective randomized multicenter study of severely preeclamptic women undergoing cesarean delivery showed that even when there was a period of increased hypotension in patients receiving spinal versus epidural anesthesia, there were no clinical differences in fetal or maternal outcomes. Aya et al. did several studies in patients with preeclampsia. In a prospective cohort study, they found that patients with severe preeclampsia had a decreased hemodynamic response to a combined spinal epidural relative to healthy patients after volume loading with 1500 mL of crystalloid. Also, Aya et al. compared healthy preterm and severely preeclamptic women undergoing cesarean delivery under spinal anesthesia. They concluded that although hypotension occurred in both groups, there are specific factors related to preeclampsia that decreased the incidence of hypotension in that group rather than the aortocaval compression alone. Dyer et al., with the use of lithium dilution cardiac output monitoring in severe preeclampsia, showed that neither spinal anesthesia nor treatment of hypotension with modest doses of phenylephrine reduces maternal cardiac output during cesarean delivery, further supporting safety in this patient population. Visalyaputra et al. showed that even when there was a period of increased hypotension in patients receiving spinal versus epidural anesthesia, there were no clinical differences in fetal or maternal outcomes. Aya et al. did several studies in patients with preeclampsia. In a prospective cohort study, they found that patients with severe preeclampsia had a decreased hemodynamic response to a combined spinal epidural relative to healthy patients after volume loading with 1500 mL of crystalloid. Also, Aya et al. compared healthy preterm and severely preeclamptic women undergoing cesarean delivery under spinal anesthesia. They concluded that although hypotension occurred in both groups, there are specific factors related to preeclampsia that decreased the incidence of hypotension in that group rather than the aortocaval compression alone. Dyer et al., with the use of lithium dilution cardiac output monitoring in severe preeclampsia, showed that neither spinal anesthesia nor treatment of hypotension with modest doses of phenylephrine reduces maternal cardiac output during cesarean delivery, further supporting safety in this patient population. Two studies compared the use of intravenous patient controlled analgesia (IVPCA) opioids with epidural analgesia for patients with severe preeclampsia. Naloxone was required in 12% of the neonates of patients receiving opioids. The NICHD trial of patients with severe preeclampsia receiving aspirin demonstrates the safety of epidural and proved no association with increased risk of cesarean delivery, pulmonary edema or renal failure.

2-General Anesthesia in Preeclampsia

It is well known that GA might be needed inevitably while performing any surgical procedure. The indications for GA include suspected placental abruption, coagulopathy, platelet count less than 80,000-100,000/μL, severe pulmonary edema, eclampsia, and severe fetal distress. The fear from GA arises from the fact that during induction and intubation, there is an increased risk of hypertension, aspiration, loss of airway, or transient neonatal depression. The maternal mortality risk after GA is seven-fold greater than after regional anesthesia. Furthermore, since preeclampsia is associated with pharyngolaryngeal edema, the risk of difficult intubation is increased markedly. Besides, patients with severe preeclampsia would be treated with magnesium sulfate which causes muscle weakness and potentiates the effect of both depolarizing and non depolarizing muscle relaxants. Since the risks of GA in the preeclamptic patients are invariably high, it is recommended to consider spinal anesthesia in emergency cases with no epidural. There are certain strategies used to decrease the response to laryngoscopy. Since it is a brief period, the use of short acting opioids and antihypertensives such as remifentanil, esmolol, and nitroglycerin is suggested. Remifentanil can be used to attenuate heart rate, BP, and catecholamine responses to laryngoscopy and endotracheal intubation in both healthy and severely preeclamptic patients undergoing GA for cesarean delivery keeping in mind the increased risk of neonatal respiratory depression. A study randomizing women with severe preeclampsia to spinal or GA for cesarean
delivery due to non-reassuring fetal heart rate found that spinal anesthesia was associated with more fetal acidosis and higher base deficit although maternal hemodynamics were similar. The reason for acidosis may be attributed to the use of ephedrine (14 mg vs 3 mg)\(^5\).

**VIII-Post Preeclampsia Outcome**

Finally, patients with preeclampsia should be monitored postpartum for BP control. They may develop long term hypertension. The risk of seizures continues in the postpartum period. In fact, 33% of seizures might occur postpartum. Thrombocytopenia may need several days to resolve\(^5\).

Preeclampsia is considered a risk marker for later life diseases such as cardiovascular and renal diseases\(^37\). It is still not proven whether it directly contributes to systemic diseases or simply unmask preexisting risk factors. A systematic review and meta-analysis of 25 trials (n = 3,488,260 women) revealed that preeclampsia is associated with increased risk for hypertension, fatal and non-fatal ischemic heart disease (particularly with onset of preeclampsia <37 W gestation), stroke and venous thromboembolism\(^38\). Aukes et al. evaluated 30 women formerly diagnosed with eclampsia, 31 women with preeclampsia, and 30 healthy women. Patients who had eclamptic seizures were shown to have deficient cognitive function including memory impairment and distractibility which may be due to some degree of cerebral white matter damage\(^39\).

In conclusion, preeclampsia is a very serious syndrome that should not be underestimated. Negligence of its nature may certainly lead to various morbidities and even mortalities.
Low back pain is considered to be chronic if it has been present for longer than three months. Chronic low back pain may originate from an injury, disease or stresses on different structures of the body. The type of pain may vary greatly and may be felt as bone pain, nerve pain or muscle pain. The sensation of pain may also vary. For instance, pain may be aching, burning, stabbing or tingling, sharp or dull, and well-defined or vague. The intensity may range from mild to severe. Many different theories try to explain chronic pain. The exact mechanism is not completely understood. The specialty of interventional pain management continues to emerge. There is a wide degree of variance in the definition and practice of interventional pain management and interventional techniques. Application of interventional techniques by multiple specialties is highly variable for even the most commonly performed procedures and treated conditions1-12.

Diagnostic Approach to Low Back Pain

Appropriate history, physical examination, and medical decision-making are essential to provide appropriate documentation and patient care. The socioeconomic issues and psychosocial factors are important in the clinical decision-making process.

Kuslich et al identified intervertebral discs, facet joints, ligaments, fascia, muscles, and nerve root dura as tissues capable of transmitting pain in the low back13. Facet joint pain, discogenic pain, nerve root pain, and sacroiliac joint pain have been proven to be common causes of pain with proven diagnostic techniques14-23. In a prospective evaluation24, the relative contributions of various structures in patients with chronic low back pain who failed to respond to conservative modalities of treatments, with lack of radiological evidence to indicate disc protrusion or radiculopathy, were evaluated utilizing controlled, comparative, diagnostic blocks. In this study, 40% of the patients were shown to have facet joint pain, 26% discogenic pain, 2% sacroiliac joint pain, and possibly, 13% segmental dural nerve root irritation. No cause was identified in 19% of the patients. If there is evidence of radiculitis, spinal stenosis, or other demonstrable causes resulting in radiculitis, one may proceed with diagnostic transforaminal or therapeutic epidural injections25. Otherwise, the approach should include the diagnostic interventions with facet joint blocks, sacroiliac joint injections, followed by discography.

Lumbar discography at the present time suffers from significant controversy with Level II-2 evidence14. In contrast, facet joint nerve blocks in the diagnosis of lumbar facet joint pain provide higher evidence with Level I or Level II-115. However, sacroiliac joint injections provide Level II-2 evidence16.
The investigation of chronic low back pain without disc herniation commences with clinical questions, physical findings, and findings of radiological investigations. Radiological investigations should be obtained if the history and physical exam findings indicate their need. Controlled studies have illustrated a prevalence of lumbar facet joint pain in 21% to 41% of patients with chronic low back pain\textsuperscript{15,17-20,24-29} and 16% in post laminectomy syndrome\textsuperscript{30}. Thus, facet joints are entertained first because of their commonality as a source of chronic low back pain, available treatment, and ease of performance of the blocks. Further, among all the diagnostic approaches in the lumbosacral spine, medial branch blocks have the best evidence (Level I) with the ability to rule out false-positives (27% to 47%) and demonstrated validity with multiple confounding factors, including psychological factors\textsuperscript{31,32}, exposure to opioids\textsuperscript{33}, and sedation\textsuperscript{34-36}. In this approach, investigation of facet joint pain is considered as a prime investigation, ahead of disc provocation and sacroiliac joint blocks. Multiple studies have indicated that facet joint pain may be bilateral in 60% to 79% of cases, involving at least 2 joints and involving 3 joints in 21% to 37% of patients\textsuperscript{26-28}. Due to the innocuous nature of lumbar facet joint nerve blocks, it is recommended that all blocks be performed in one setting. However, based on the clinical examination, only 2 blocks are performed provided the first block was positive, thus avoiding a screening block and repeat blocks for separate joints\textsuperscript{37}. If a patient experiences at least 80% relief with the ability to perform previously painful movements within a time frame that is appropriate for the duration of the local anesthetic used and the duration of relief with the second block relative to the first block is commensurate with the respective local anesthetic employed in each block, then a positive diagnosis is made.

The sacroiliac joint as the pain generator, pain must be caudal to L5 and must be positive with flexion and abduction of the hip, along with tenderness over the sacroiliac joint on palpation\textsuperscript{16,38,39}. Sacroiliac joint blocks have a Level II-2 evidence in the diagnosis of sacroiliac joint pain utilizing comparative controlled local anesthetic blocks. The prevalence of sacroiliac joint pain is estimated to range between 2% and 38% using a double block paradigm in specific study populations\textsuperscript{16,21,22,24,39-44}. The false-positive rates of single, uncontrolled, sacroiliac joint injections have been shown to be 20% to 54%\textsuperscript{16}. However, there has been a paucity of the evidence in the evaluation of the effectiveness of sacroiliac joint blocks in the diagnosis of sacroiliac joint pain\textsuperscript{16,21,22}. The relief obtained should be 80% with the ability to perform previously painful movements and also should be concordant based on the local anesthetic injection\textsuperscript{16,38}.

If pain is not suggestive of facet joint or sacroiliac joint origin, then an epidural is to be considered. Caudal and lumbar interlaminar epidurals are non-specific as far as identifying the source of pain. If a patient fails to respond to epidural injections, the discogenic approach may be undertaken.

Provocation lumbar discography is performed as the first test in only specific settings of suspected discogenic pain and availability of a definitive treatment is offered solely for diagnostic purposes prior to fusion. Otherwise, once facet joint pain, and if applicable sacroiliac joint pain, is ruled out and the patient fails to respond to at least 2 fluoroscopically directed epidural injections, discography may be pursued if determination of the disc as the source of pain is crucial. Moreover, lumbar provocation discography is the last step in the diagnostic algorithm and is utilized only when appropriate treatment can be performed if disc abnormality is noted. Magnetic resonance imaging (MRI) will assist in ruling out any red flags and disc herniation, but will not determine if the disc is the cause of the pain. Lumbar provocation discography has been shown to reveal abnormalities in asymptomatic patients with normal MRI scans\textsuperscript{45,46}. Thus, when performed appropriately, discography can enhance sensitivity and specificity compared to non-provocational imaging. Discography continues to be the only diagnostic tool capable of establishing whether or not a particular disc is painful, irrespective of the presence or absence of degenerative pathology observed on other imaging.
modalities. Provocation discography continues to be controversial with respect to diagnostic accuracy, utilization, and its impact on surgical volume. However, lumbar discography has been refined substantially since its inception and its diagnostic accuracy has been established as Level II. In order to be valid, the provocation discography must be performed utilizing strict criteria of having concordant pain in one disc with at least 2 negative discs, one above and one below except when the L5/S1 is involved. Studies have shown the effectiveness of epidural injections in discogenic pain, with or without the use of steroids, after facet joint pain and other sources of low back pain have been eliminated. In addition, the relief derived from discogenic pain with caudal epidural injections, with or without steroids, was equivalent to relief in managing disc herniation and superior to the relief obtained by patients with either spinal stenosis or post lumbar laminectomy syndrome.

Given the realities of health care in the United States and the available evidence from the literature, it appears that lumbar facet joints account for 30% of cases of chronic low back pain, sacroiliac joint pain accounts for less than 10% of cases, and discogenic pain accounts for 25% of cases.

Approximately 70% of low back pain patients would undergo investigations of their facet joints, with approximately 30% proving positive and requiring no other investigations. Of the 70% remaining, approximately 10% will require sacroiliac joint blocks and perhaps 30% will prove to be positive. The remaining 60% of 70% and original 30% not undergoing facet injections - overall 60% to 70% - will probably undergo epidural injections and approximately 65% will respond to epidural injections and the remaining 20% of 35% will be candidates for provocation discography if a treatment can be provided.

Treatment of Somatic Pain

The patients testing positive for facet joint pain may undergo either therapeutic facet joint nerve blocks or radiofrequency neurotomy based on the patients’ preferences, values, and physician expertise. However, there is no evidence for lumbar intraarticular facet joint injections. In contrast, based on the review of included therapeutic studies, Level I-1 to II-2 evidence is presented for lumbar facet joint nerve blocks with an indicated level of evidence of II-2 to III-3 for lumbar radiofrequency neurotomy.

The next modality of treatment is epidural injections. Epidural injections have been shown to present with variable evidence. A recent systematic review of caudal epidural injections in the management of chronic low back pain showed Level I evidence for relief of chronic pain secondary to disc herniation or radiculitis and discogenic pain without disc herniation or radiculitis. Further, the indicated evidence was Level II-1 or II-2 for caudal epidural injections in managing chronic pain of post lumbar surgery syndrome and spinal stenosis.

The indicated evidence for therapeutic sacroiliac joint interventions is Level II-2 with no evidence for sacroiliac joint neurotomy.

Treatment of Radicular Pain

While disc protrusion, herniation, or prolapsed resulting in sciatica are seen in less than 5% of the patients with low back pain, approximately 30% of the patients presenting to interventional pain management clinics will require either caudal, interlaminar, or transforaminal epidural injections as an initial treatment.
Many patients with post-surgery syndrome, spinal stenosis, and radiculitis without disc protrusion may respond to epidural injections. Patients non-responsive to epidural injections will require either mechanical disc decompression, percutaneous adhesiolysis, spinal endoscopic adhesiolysis, implantation of spinal cord stimulation, or intrathecal infusion systems depending on the clinical presentation, pathology, and other biopsychosocial factors. Transforaminal epidural injections may be performed for diagnostic purposes; however, these also lead to therapeutic improvement. Buenaventura et al in a systematic review of therapeutic lumbar transforaminal epidural steroid injections showed the indicated level of evidence as II-1 for short-term relief of 6 months or less and Level II-2 for long-term relief of longer than 6 months in managing chronic low back and lower extremity pain. Conn et al in a systematic review of caudal epidural injections in the management of chronic low back and lower extremity pain showed variable evidence for various conditions causing low back and lower extremity pain. The evidence level shown is Level I for short- and long-term relief in managing chronic low back and lower extremity pain secondary to lumbar disc herniation and radiculitis and discogenic pain without disc herniation or radiculitis. The indicated level of evidence is Level II-1 or II-2 for caudal epidural injections in managing low back pain of post-lumbar laminectomy syndrome and spinal stenosis.

In contrast to lumbar transforaminal and caudal epidural injections, the evidence for lumbar interlaminar epidural injections in managing chronic low back and lower extremity pain is limited due to the lack of availability of studies utilizing fluoroscopy. The evidence is delivered from blind interlaminar epidural injections. Based on Parr et al’s systematic review, the indicated evidence is Level II-2 for short-term relief of pain of disc herniation or radiculitis utilizing blind interlaminar epidural steroid injections with a lack of evidence with Level III for long-term relief of disc herniation and radiculitis. Furthermore, the evidence at present is lacking for short- and long-term relief of spinal stenosis and discogenic pain without radiculitis or disc herniation utilizing blind epidural injections.

If a patient presents with unilateral, single, or 2 level involvement, one may proceed with transforaminal epidural injections (diagnostic and therapeutic). Bilateral or extensive involvement of multiple segments will lead to either interlaminar or caudal based on the upper or lower levels being involved, extensive stenosis (central or foraminal) and lack of response to caudal or interlaminar approaches. Except in specific documented circumstances with spinal stenosis, the approach also is based on the same philosophy as described above for transforaminal epidurals. For postsurgery syndrome, a caudal epidural is preferred and one may consider a transforaminal epidural if essential in patients without obstructing hardware.

The evidence for intradiscal procedures with thermal annular technology is also limited. The systematic review of the effectiveness of thermal annular procedures in treating discogenic low back pain showed an indicated level of evidence of II-2 for IDET, Level II-3 for radiofrequency annuloplasty, and limited or lack of evidence for intradiscal biacuplasty.

**Treatment of Chronic Pain Non Responsive to Conventional Management**

Patients non-responsive to epidural injections may be considered for mechanical disc decompression, percutaneous adhesiolysis, spinal endoscopic adhesiolysis, spinal cord stimulation, or implantation of intrathecal infusion systems.

Percutaneous mechanical disc decompression lacks evidence. There are 4 modalities, namely automated percutaneous lumbar discectomy, percutaneous laser discectomy, a high RPM device utilizing Dekompressor,
and coblation nucleoplasty or plasma decompression. Recent systematic reviews showed the evidence to be Level II-2 for short- and long-term (> 1 year) improvement for percutaneous automated lumbar discectomy and laser discectomy. The evidence for coblation nucleoplasty (Level II-3) and Dekompressor (Level III) is only emerging.

In patients with post-lumbar surgery syndrome after failure to respond to fluoroscopically directed epidural injections, percutaneous adhesiolysis is considered. Despite a paucity of efficacy and pragmatic trials, the systematic review by Epter et al indicated the evidence as Level I or II-1 with short term relief being considered as 6 months or less and long-term longer than 6 months, in managing post-lumbar laminectomy syndrome. Another type of adhesiolysis is spinal endoscopic adhesiolysis, which is considered to be an experimental procedure. It also showed the indicated level of evidence of II-1 for short-term and Level III for long-term relief (≤ 6 months or > 6 months).

The next step in the radicular pain is implantable therapy. Frey et al in a systematic review of spinal cord stimulation for patients with failed back surgery syndrome (FBSS) indicated the level of evidence as II-1 or II-2 for long-term relief (> 1 year) in managing patients with FBSS. In this systematic review, 2 randomized trials and 8 observational studies were included. Despite early increased expense, cost-effectiveness has been demonstrated for spinal cord stimulation.

Finally, long-term management of chronic noncancer pain may be achieved with intrathecal infusion systems. Intrathecal infusion systems are also utilized for non-cancer pain in FBSS as an advanced stage intervention. While there is a lack of conclusive evidence due to the paucity of quality literature, Patel et al concluded that the level of evidence for intrathecal infusion systems was indicated as Level II-3 or Level III with longer than one-year improvement considered as long-term response.

**Interventional Pain Management**

There is no consensus among interventional pain management specialists with regards to type, dosage, frequency, total number of injections, or other interventions. The literature provides some guidance even though not conclusive. The recent literature shows no significant difference in the outcomes with or without steroids with medial branch blocks and epidural injections. Many of the techniques including radiofrequency neurolysis and disc decompressions do not require any steroids.

The most commonly used formulations of long acting steroids include methylprednisolone (Depo-Medrol), triamcinolone acetonide (Aristocort or Kenalog), and betamethasone acetate. Soon after the historic introduction of cortisone in 1949, steroids were used for various other purposes including placement in the epidural space, facet joints, sacro-iliac joints, and for infiltration of other nerves. The first published report of the injection of steroids into an arthritic joint was in 1951, followed by the application of transforaminal epidural steroid injections in 1952 and 1953. Since then, the use of spinal steroids has been reported with various approaches. Simultaneous with the introduction of neuraxial steroids in interventional pain management, various complications related to steroid therapy, including systematic effects of particulate steroids, have been described with increasing frequency, cautioning against use of spinal steroids in interventional pain management. The rationale for the use of epidural steroids into various joints and epidural space has been based on the strong anti-inflammatory effects of corticosteroids. However, while inflammation is an issue with discogenic pain and radiculitis, no
inflammation has been proven to be present in other cases. It is postulated that corticosteroids reduce inflammation either by inhibiting the synthesis of or release of a number of pro-inflammatory substances or by causing irreversible local anesthetic effect on C-fibers\textsuperscript{141-156}. The role of epidural steroids has been evaluated in experimental models with betamethasone reducing the nerve root injury produced by epidural application\textsuperscript{146,149}, with suppression of disc resorption by high dose steroids\textsuperscript{153}, the depression of heat hyperalgesia and mechan- allodynia\textsuperscript{155}, prevention of neuropathic edema and blockade of neurogenic extravasation\textsuperscript{154}, inhibition of phospholipase A\textsubscript{2} activity\textsuperscript{150}, protection of C-fibers from damage\textsuperscript{151}, prevention of endoneural vascular permeability induced by nucleus pulposus\textsuperscript{152}, and decrease of the extent of intramedullary spinal cord injury secondary to spinal cord hemorrhage\textsuperscript{156}. The chemistry of neuraxial steroids has taken center stage in recent years due to devastating complications following epidural injections, specifically transforaminals\textsuperscript{128-131,157-168,169}. Steroid particle embolization into small radicular arteries is believed to be an important causative factor\textsuperscript{131,163}. Tiso et al\textsuperscript{128} and Benzon et al\textsuperscript{129} extensively evaluated chemical properties and their relationship to interventional pain management. Data from Tiso et al and Benzon et al regarding particle sizes were in general agreement with regards to methylprednisolone, triamcinolone, and commercial betamethasone. However, there were some differences pertaining to dexamethasone and betamethasone sodium phosphate. Nonetheless, based on the available literature and scientific applications, all the formulations of steroids may be considered clinically safe; however important physiochemical characteristics distinguish one compound from the others (Table 1). Though all formulations of steroids may be considered safe, formulations of betamethasone appear to be safer with no significant difference in the effectiveness\textsuperscript{127}. Formulations of commonly used epidural steroids are shown in Table 1 and the pharmacologic profile of commonly used epidural steroids is shown in Table 1.

Steroids lead to suppression of the hypothalamic pituitary axis with decreased plasma cortisol, decreased plasma adrenocorticotropic hormone (ACTH), and adrenal atrophy\textsuperscript{127,170,171}. Other side effects may be specific to the site of injection which includes arachnoiditis, intrathecal injection, and particulate embolism. Numerous arguments of steroid toxicity to the nervous system stem from the potential toxicity of multiple chemical entities used mostly as preservatives in the formulations of epidural steroids. Nelson\textsuperscript{132} spearheaded the crusade against intraspinal therapy using steroids and argued that methylprednisolone acetate was neurotoxic. Betamethasone does not contain either polyethylene glycol or benzyl alcohol.

Similarly, single dose vials of methylprednisolone (DepoMedrol) are available without alcohol. Latham et al\textsuperscript{119} reported that when injected deliberately into the subarachnoid space in sheep, betamethasone caused no reaction in the meninges or neural structures when small doses of 1 mL were used, even on repeated occasions. Other central nervous system (CNS) events described are worrisome. These are based on the particle size of epidural steroids and the risk of vascular obstruction and ischemic CNS injury as a result of embolization. There have been several reported cases of CNS injuries after transforaminal epidural injections\textsuperscript{172,173,128,129,160-167}. One of the postulated mechanisms of these events is occlusion of the segmental artery accompanying the nerve root by the particulate steroid or embolization of the particulate steroid through the vertebral artery\textsuperscript{128,129,165,168,171}. Consistent with the present literature of the pharmacology of steroids, it appears that non-particulate steroids may be the agents of choice for transforaminal epidural injections, though no trials have compared particulate to non-particulate steroids. However, particulate steroids may be safely utilized for interlaminar or caudal epidural injections. Caution must be exercised in the use of particulate steroids in transforaminal epidural injections and specifically for cervical transforaminal epidural injections, particularly if sharp needles are used.

The frequency and total number of injections have been considered important issues, even though
controversial and poorly addressed. These are based on flawed assumptions from non-existing evidence. Over the years, some authors have recommended one injection for diagnostic as well as therapeutic purposes. Some have preached 3 injections in a series, irrespective of a patient’s progress or lack thereof, whereas others suggest 3 injections followed by a repeat course of 3 injections after 3-, 6-, or 12-month intervals. There are also proponents of an unlimited number of injections with no established goals or parameters. A limitation of 3 mg per kilogram of body weight of steroid or 210 mg per year in an average person and a lifetime dose of 420 mg of steroid also have been advocated, however, with no scientific basis. The review of the literature and of all the systematic reviews has not shown any basis for the above reported assumptions and limitations. The administration must be based solely on the patients’ responses, safety profile of the drug, experience of the physician, and pharmacological and chemical properties such as duration of action and suppression of adrenals.

**Table 1**

**Epidural Steroids**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Equivalent Dose</th>
<th>Epidural Dose</th>
<th>Anti-Inflammatory Potency</th>
<th>Sodium Retention Capacity</th>
<th>Duration of adrenal Suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>20 mg</td>
<td>N/A</td>
<td>1</td>
<td>1</td>
<td>N/A</td>
</tr>
<tr>
<td>Depo-Methylprednisolone</td>
<td>4 mg</td>
<td>40–80 mg</td>
<td>5</td>
<td>0.5</td>
<td>1–6 weeks</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>4 mg</td>
<td>40–80 mg</td>
<td>5</td>
<td>0</td>
<td>2–6 weeks</td>
</tr>
<tr>
<td>Dexamethasone (Decadron)</td>
<td>0.75 mg</td>
<td>8–16 mg</td>
<td>27</td>
<td>1</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A = Not available


**Indication and Frequency of Interventional Pain Management Techniques**

Some criteria should be considered carefully before performing any interventional technique. The physician has to complete an initial evaluation, including history and physical examination, with a psychosocial and functional assessment. The indications are a suspected organic problem, nonresponsiveness to less invasive modalities of treatments except in acute situations such as acute disc herniation, herpes zoster, complex regional pain syndrome (CRPS), and intractable cancer-related pain. These techniques are applied when the pain and disability are of moderate-to-severe degree and when there is no contraindication such as severe spinal stenosis resulting in intraspinal obstruction, infection, impaired coagulation, or predominantly psychogenic pain. The responsiveness to prior interventions with improvement in physical and functional status is a must to justify repeat blocks or other interventions. The interventions are repeated only upon return of pain and deterioration in functional status with a documented decreased pain and increased function after the initial intervention. The indications are variable for various types of interventional techniques.

**Facet Joint Interventional Procedures**
Lumbar facet joints are a well-recognized source of low back and referred pain in the lower extremity in patients with chronic low back pain. Facet joints are well innervated by the medial branches of the dorsal rami. Kalichman et al evaluated facet joint osteoarthritis and low back pain in the community-based Framingham Heart Study. They concluded that there is a high prevalence of facet joint osteoarthritis in the community-based population with a prevalence of 59.6% in males and 66.7% in females. The prevalence of facet joint osteoarthritis increased with age and reached 89.2% in individuals 60 to 69 years old with highest prevalence of facet joint osteoarthritis found at the L4/5 spinal level. Facet joint pain may be managed by intraarticular injections, facet joint nerve blocks, and neurolysis of facet joint nerves. Facet arthrosis has been suggested as a cause of low back pain for decades. However, the exact source of pain in the facet joints is ambiguous. Theories on the generation of pain range from mechanical alterations to vascular changes and molecular signaling. While disc degeneration can clearly cause low back pain, some patients may not experience pain until degenerative changes in the facet joints alter mechanical alignment sufficiently to produce “articular” low back pain. Most publications agree that 2 diagnostic blocks must be performed before radiofrequency denervation and many payors are requiring 80% or more pain relief. Consequently, a single block will definitely increase costs of care as the single diagnostic block will lead to an increase in number of radiofrequency denervations, which are more expensive and time consuming. The most common and worrisome complications of facet joint interventions are related to needle placement and drug administration. Potential complications include dural puncture, spinal cord trauma, infection, intraarterial or intravenous injection, spinal anesthesia, chemical meningitis, neural trauma, pneumothorax, radiation exposure, facet capsule rupture, hematoma formation, and steroid side effects. Potential side effects with radiofrequency denervation include painful cutaneous dysesthesias, increased pain due to neuritis or neurogenic inflammation, anesthesia dolorosa, cutaneous hyperesthesia, pneumothorax, and deafferentation pain. Unintentional damage to a spinal nerve during medial branch radiofrequency, causing a motor deficit, is also a complication of a neurolytic procedure.

Common indications for diagnostic facet joint interventions are somatic or nonradicular low back, midback, or upper back and/or lower extremity pain. This pain should be intermittent or continuous in nature, causing functional disability and is present at least for the past 3 months. Those blocks are performed after eliminating a disc herniation or evidence of radiculitis and when more conservative management, including physical therapy modalities with exercises, chiropractic management, and nonsteroidal anti-inflammatory agents fails.

In the diagnostic phase, a patient may receive two procedures at intervals of no sooner than one week or preferably two weeks, with careful judgment of response. A positive response to controlled local anesthetic blocks (< 1mL) is associated with 80% pain relief and the ability to perform prior painful movements without any significant pain. In the therapeutic phase (after the diagnostic phase is completed), the suggested frequency would be two to three months or longer between injections, provided that ≥ 50% relief is obtained for 6–8 weeks. If the interventional procedures are applied for different regions, they may be performed at intervals of no sooner than one week or preferably two weeks for most types of procedures. It is suggested that therapeutic frequency remain at least a minimum of 2 months for each region; it is further suggested that all the regions be treated at the same time provided that all procedures can be performed safely. In the treatment or therapeutic phase, facet joint interventions should be repeated only as necessary according to the medical necessity criteria, and it is suggested that these be limited to a maximum of 4 to 6 times for local anesthetic and steroid blocks over a period of one year, per region. Under unusual circumstances with a recurrent injury, procedures may be repeated at intervals of 6 weeks after stabilization in the treatment phase. For medial branch neurotomy, the
suggested frequency would be 3 months or longer (maximum of 3 times per year) between each procedure, provided that 50% or greater relief is obtained for 10 to 12 weeks. The therapeutic frequency for medial branch neurotomy should remain at intervals of at least 3 months per each region with multiple regions involved. It is further suggested that all regions be treated at the same time, provided all procedures are performed safely.

**Epidural Infiltrations**

Epidural injections in the lumbar spine are provided by caudal, lumbar interlaminar, or transforaminal routes. While interlaminar entry is considered to deliver the medication closely to the assumed site of pathology, the transforaminal approach is considered as target-specific requiring the smallest volume to reach the primary site of pathology. Caudal epiduals are considered as the safest and easiest, with minimal risk of inadvertent dural puncture, even though requiring relatively high volumes. They have also been shown to be significantly effective compared to interlaminar epidural injections.\(^{181,182}\) Even then, controversy continues with regards to the medical necessity and indications of lumbar epidural injections. These guidelines apply to all epidural injections including caudal, interlaminar, and transforaminal.

Complications and side effects include infection, intravascular injection, extra epidural placement, hematoma formation, abscess formation, subdural injection, intracranial air injection, epidural lipomatosis, dural puncture, nerve damage, headache, increased intracranial pressure, vascular injury, cerebral vascular or pulmonary embolus and effects of steroids.

**Caudal**

The caudal approach to the epidural space via the sacral hiatus is often the preferred injection method in the treatment of low back pain caused by lumbosacral root compression. Many nonanesthetists prefer this injection method because it carries a lower risk of inadvertent thecal sac puncture and intrathecal injection. Successful caudal epidural injection relies on the proper placement of the needle in the epidural space. The most common method used to identify the caudal epidural space is by detecting the characteristic “give” or “pop” when the sacrococcygeal ligament is penetrated. In the event of unaided or blind needle insertion, incorrect needle placement has been reported to occur in 25% to 38% of cases, even in the hands of experienced physicians. Furthermore, even when physicians are confident with their injection technique, incorrect needle placement has been observed in about 1 of 7 caudal injection procedures. An incorrect needle position would most likely result in deep subcutaneous injections. In clinical practice, the “whoosh” test, nerve stimulation, and fluoroscopy are the 3 methods that can be used to identify the caudal space before the injection of medications. Approximately 3% of the studied population has closed sacral canals, thus making caudal epidural injections impossible for these subjects.

The common indications are chronic low back and/or lower extremity pain which has failed to respond or poorly responded to noninterventional and nonsurgical conservative management resulting from disc herniation, lumbar radiculitis, lumbar spinal stenosis, post lumbar surgery syndrome, epidural fibrosis, degenerative disc disease and discogenic low back pain. The facet joint pain should be eliminated by controlled local anesthetic blocks.
**Lumbar Interlaminar**

In a randomized, double-blind, controlled trial of lumbar interlaminar epidural injections in chronic function-limiting low back pain without facet joint pain, disc herniation, and/or radiculitis, Manchikanti et al demonstrated an effectiveness in 74% of the patients receiving local anesthetic only and 63% of patients receiving local anesthetic and steroids with an average of 4 procedures per year.

The indications are the same as for caudal epidural injections, except for post-surgery syndrome where caudal epidural is the modality of choice.\(^{183}\)

**Lumbar Transforaminal**

Lumbar transforaminal epidurals are provided for diagnostic and therapeutic purposes. The aim of the diagnostic procedure is to identify an inflamed nerve root in a patient with a history of radicular pain when results of visual anatomic studies and neurophysiologic studies are not collaborative. It also helps to identify the pain generator when patients have multiple abnormalities on visual anatomic studies and to determine a primary pain generator in the spine-hip syndrome, the symptomatic level in multilevel disc herniation or stenosis and the irritated root in patients with documented postoperative fibrosis or spondylolisthesis.

The therapeutic indications are an intermittent or continuous pain causing functional disability. A chronic low back and/or lower extremity pain which has failed to respond or poorly responded to non-interventional and non-surgical conservative management, resulting from disc herniation, failed back syndrome without extensive scar tissue and hardware, spinal stenosis with radiculitis and discogenic pain with radiculitis.

The guidelines of frequency of interventions apply to epidural injections caudal, interlaminar, and transforaminal. In the diagnostic phase, a patient may receive two procedures at intervals of no sooner than one week or preferably two weeks except in cancer-related pain or when a continuous administration of local anesthetic is employed for CRPS.

In the therapeutic phase (after the diagnostic phase is completed), the suggested frequency of interventional techniques should be two months or longer between each injection, provided that > 50% relief is obtained for six to eight weeks. If the neural blockade is applied for different regions, they may be performed at intervals of no sooner than one week and preferably two weeks for most types of procedures. The therapeutic frequency may remain at intervals of at least two months for each region. It is further suggested that all regions be treated at the same time, provided all procedures can be performed safely. In the treatment or therapeutic phase, the epidural injections should be repeated only as necessary according to medical necessity criteria, and it is suggested that these be limited to a maximum of 4–6 times per year. Under unusual circumstances with a recurrent injury, cancer-related pain, or CRPS, blocks may be repeated at intervals of 6 weeks or less after diagnosis/stabilization in the treatment phase.

**Percutaneous Adhesiolysis**

Adhesiolysis of epidural scar tissue, followed by the injection of hypertonic saline, has been described by Racz and coworkers in multiple publications. The technique described by Racz and colleagues involved epidurography, adhesiolysis, and injection of hyaluronidase, bupivacaine, triamcinolone diacetate, and 10%
sodium chloride solution on day one, followed by injections of bupivacaine and hypertonic sodium chloride solution on days 2 and 3. Manchikanti and colleagues modified the Racz protocol from a 3-day procedure to a one-day procedure. The goal of percutaneous lysis of epidural adhesions is to assure delivery of high concentrations of injected drugs to the target areas. Thus, percutaneous epidural lysis of adhesions is the first and most commonly used treatment to incorporate multiple therapeutic goals. Inflammation, edema, fibrosis, and venous congestion; mechanical pressure on posterior longitudinal ligaments, annulus fibrosus, and spinal nerve; reduced or absent nutrient delivery to the spinal nerve or nerve root; and central sensitization may be present in patients with radiculitis with disc herniation, stenosis, and epidural fibrosis. Hence, it has been postulated as reasonable to treat back pain with or without radiculopathy with the local application of anti-inflammatory medication agents (e.g., corticosteroids) aimed at reducing edema (e.g., hypertonic sodium chloride solution, corticosteroids), local anesthetics, and hyaluronidase to promote lysis. Thus, percutaneous lysis of adhesions is indicated in patients with appropriate diagnostic evaluation and after the failure or ineffectiveness of conservative modalities of treatment have been proven.

The most common and worrisome complications of adhesiolysis in the lumbar spine are related to dural puncture, spinal cord compression, catheter shearing, infection, steroids, hypertonic saline, and hyaluronidase. Spinal cord compression following rapid injections into the epidural space, which may cause large increases in intraspinal pressure with a risk of cerebral hemorrhage, visual disturbance, headache, and compromise of spinal cord blood flow, has been mentioned.

The indications for an epidural adhesiolysis are chronic low back and/or lower extremity pain resulting from a failed back surgery syndrome or epidural fibrosis, spinal stenosis, disc herniation with radiculitis and failure to respond or poor response to noninterventional and non-surgical conservative management and fluoroscopically-directed epidural injections. Adhesiolysis can be performed after eliminating a facet joint pain by controlled local anesthetic blocks. The number of procedures is preferably limited to two interventions per year.

**Spinal Endoscopic Adhesiolysis**

There is insufficient evidence to conclude that epiduroscopy can improve patient management or disease outcomes. The available studies primarily evaluated the feasibility of the procedure and the ability to visualize normal and pathological structures with an epiduroscope. Some studies concluded that epiduroscopy could identify the cause of pain and other neurological signs in some patients who had been either undiagnosed or incorrectly diagnosed by radiography or magnetic resonance imaging (MRI). Geurts et al. reported that epiduroscopy outperformed MRI in 8 out of 20 patients with chronic sciatica with or without failed back syndrome (Geurts, 2002). In this study, MRI findings agreed with epiduroscopy observations in 11 patients, while epiduroscopy identified an adhesion on the nerve root in 8 patients in whom MRI detected no abnormalities of the spinal structures. There is insufficient evidence to conclude that epidural lysis of adhesions can provide sustained reduction in chronic back pain in patients with a presumptive diagnosis of epidural adhesions. The common indications of this procedure are chronic low back and lower extremity pain nonresponsive or poorly responsive to conservative treatment, including fluoroscopically directed epidural injections and percutaneous adhesiolysis with hypertonic saline neurolysis. The procedures are preferably limited to a maximum of two per year provided the relief was > 50% for > 4 months.
Intradiscal Procedures

The lumbar intervertebral discs have been shown to be sources of chronic back pain without disc herniation in 26% to 39%. Lumbar provocation discography, which includes disc stimulation and morphological evaluation, is often used to distinguish a painful disc from other potential sources of pain. Conversely, there is evidence that subtle but painful lesions may be present in discs that appear morphologically normal on MRI. Discography has been shown to reveal abnormalities in symptomatic patients with normal MRI scans. Lei et al concluded that MRI should continue to supplement discography rather than replace it. In a meta-analysis by Wolfer et al, the authors concluded that the false-positive rate was acceptably low and indicated the level of evidence for discography was Level II-2. In a therapeutic attempt, a steroid might be injected to decrease inflammation and swelling that may be present within a disc. The steroid usually starts to work in 2-3 days, but the optimal effects are not known until 1-2 weeks after the injection. The duration and extent of pain relief from therapeutic intradiscal injection is associated with variable results. The indications are axial low back pain of at least 6 months duration with failure to respond to conservative treatment, abnormal nucleus signal on T2-weighted MRI images with > 60% residual disc height and no evidence of root compression, tumor, or infection. Finally, even though lumbar provocation discography with a double needle technique is considered safe, discitis is a serious problem. Further, needle puncture injury was shown to affect intervertebral disc mechanics and biology in an organ culture model. In addition, incidence of intravascular uptake during fluoroscopically guided lumbar disc injections also has been demonstrated.

Mechanical Disc Decompression

Lumbar disc prolapse, protrusion, or extrusion account for less than 5% of all low back problems, but are the most common causes of nerve root pain and surgical interventions. The primary rationale for any form of surgery for disc prolapse is to relieve nerve root irritation or compression due to herniated disc material. The primary modality of treatment continues to be either open or microdiscectomy, but several alternative techniques including nucleoplasty, automated percutaneous discectomy, and laser discectomy have been described. Disc herniations consist of both contained and non-contained types. While for non-contained disc herniations, open discectomy is the approach of choice, partial removal of the nucleus pulposus in contained discs has been shown to decompress herniated discs and relieve pressure on nerve roots in a much less invasive manner.

Nucleoplasty, a minimally invasive procedure, uses radiofrequency energy to remove nuclear material and create small channels within the disc. Nucleoplasty utilizing Coblation technology dissolves the nuclear material through molecular dissociation, and is thought to lower nuclear pressure, thereby reducing the nerve root tension and allowing a protrusion to implode inward. However, epidural fibrosis may develop with nucleoplasty. At present, the common indication is unilateral leg pain with radicular symptoms in a specific dermatomal distribution that correlates with MRI findings. Imaging studies (CT, MRI, discography) should indicate a subligamentous contained disc herniation with a well maintained disc height of 60%. Nucleoplasty may be considered prior to open discectomy, however, automated percutaneous lumbar discectomy and laser discectomy have been shown to have better evidence with extensive experience.

Sacroiliac Joint Injections
The sacroiliac joint is a diarthrodial joint, receiving innervation from the lumbosacral nerve roots. Controlled local anesthetic blocks continue to be the best available tool to identify either the intervertebral discs, facet, or sacroiliac joints as the source of low back pain. Sacroiliac joint pain may be managed by intraarticular injections or neurolysis of the nerve supply. A retrospective review by Borowsky and Fagen conducted in 120 patients found the combination of intra- and peri-articular injectate deposition provided superior analgesia than intraarticular injection alone.

The common indications are somatic or nonradicular low back and lower extremity pain below the level of L5 vertebra which failed to respond to more conservative management, including physical therapy modalities with exercises, chiropractic management, and non-steroidal anti-inflammatory agents. For therapeutic sacroiliac joint interventions with intraarticular injections or radiofrequency neurotomy, the joint should have been positive utilizing controlled diagnostic blocks.

In the diagnostic phase, a patient may receive two SI joint injections at intervals of no sooner than one week or preferably two weeks. In the therapeutic phase (after the diagnostic phase is completed), the suggested frequency would be two months or longer between injections, provided that > 50% relief is obtained for six weeks. If the procedures are done for different joints, they should be performed at intervals of no sooner than one week or preferably two weeks. It is suggested that therapeutic frequency remain at two months for each joint. It is further suggested that both joints be treated at the same time, provided the injections can be performed safely. In the therapeutic phase, the interventional procedures should be repeated only as necessary according to the medical necessity criteria, and it is suggested that they be limited to a maximum of 4 – 6 times for local anesthetic and steroid blocks over a period of one year, per region. Under unusual circumstances with a recurrent injury, procedures may be repeated at intervals of six weeks after stabilization in the treatment phase. For sacroiliac joint radiofrequency neurotomy the suggested frequency is three months or longer between each procedure (maximum of 3 times per year), provided that > 50% relief is obtained for 10 to 12 weeks.

**Trigger-Point and Ligamental Injections**

Limited evidence was found suggesting that a combination of corticosteroid injections and local anaesthetic injections in trigger points and phenol-injections in lumbar ligaments were effective in chronic low back pain. One RCT (n=57) compared ‘trigger-point’ injections with methyl-prednisolone plus lidocaine versus triamcinolone plus lidocaine versus lidocaine alone. 60-80% of patients with a combination of lidocaine and corticosteroid had complete relief of pain after three months compared to 20% in the lidocaine group. The other RCT (n=81) compared ligamental dextrose-glycerine-phenol injections with saline. The decrease in pain and improvement in functional status was larger with phenol than with saline at one, three and six months.

**Spinal Cord Stimulator**

Patients may have persistent disabling low back pain despite use of several standard therapies or following back surgery (ie, failed back surgery syndrome). Chronic opioids may be used in such patients to manage pain, but responses are incomplete, long-term outcome unknown, and side effects can be serious. Opioids should only be used after adequate risk assessment and with appropriate monitoring and supervision. Spinal cord stimulation involves the placement of electrodes in the epidural space adjacent to the spinal area.
presumed to be the source of pain. An electric current is then applied to achieve sympatholytic and other neuromodulatory effects. The resulting impulses in the fibers may inhibit the conduction of pain signals to the brain according to the pain gate theory. Moreover, the number and type of leads (unipolar, bipolar, or multipolar) and the parameters of stimulation (amplitude pulse width electrode sensation) may vary depending on the nerve roots involved and the intensity of the pain being experienced by the patient. Further, the electrodes may be implanted percutaneously or by laminectomy, and power for the spinal cord stimulator is supplied by an implanted battery or transcutaneously through an external radiofrequency transmitter. The implanted source of power is equipped with a computerized telemetry system that allows transcutaneous programming of the specific pattern of stimulation. In the randomized trials, 26 to 32 percent of patients experienced a complication following spinal cord stimulator implantation, including electrode migration, infection or wound breakdown, generator pocket-related complications, and lead problem. Currently, the common indications for a spinal cord stimulator implantation are a documented lumbosacral arachnoiditis that has not responded to medical management. The best candidates are those with intractable pain caused by nerve root injuries, including the postlaminectomy syndrome, this umbrella term overlies a constellation of different symptoms and etiologies, predominantly neuropathic extremity pain. Demonstration of pain relief stipulates a screening period using temporary percutaneous placement of leads and an external generator.

**Intrathecal Pump Insertion**

Intrathecal drug delivery systems are implanted for chronic pain when conservative therapies have failed, surgery is ruled out, no active or untreated addiction exists, psychological testing indicates appropriateness for implantable therapy, medical contraindications have been eliminated (coagulopathies, infections), and a successful intrathecal drug trial has been completed. Intrathecal pumps deliver small doses of medication directly to the spinal fluid. It consists of a small battery-powered, programmable pump that is implanted under the subcutaneous tissue of the abdomen and connected to a small catheter tunneled to the site of spinal entry. Sophisticated drug dose regimens can be instituted. Implanted pumps need to be refilled every 1 to 3 months. There is no evidence showing whether it is more clinically effective to use bolus or continuous dosing. No intrathecal device should be implanted for pain management of chronic low back pain without first performing a trial. This phase determines whether a patient will benefit from an implant. The first line of treatment includes morphine and hydromorphone. The second protocol may actually be chosen as first line in cases where an individual has prominently neuropathic symptoms. This consists of either hydromorphone or morphine with the addition of bupivacaine or clonidine. After failure of first and second line drug combination treatments, either due to intolerable side effects or inadequate analgesia, the physician might consider using lipophilic opioid agents such as fentanyl and gamma-aminobutyric acid (GABA) agonists such as baclofen and midolazam. Bleeding, neurological injury, infection, cerebral spinal leaks, shredded catheters, and malpositioned subcutaneous pockets are the surgical complications during the insertion of an intrathecal pump. Drug refills must be done by trained individuals who are able to accurately assess pain and subtle changes in the patient condition. Drug tolerance is caused by psychological, pharmacological or physiological aspects and can best be described as the need for dose escalation for equivalent effect. A Canadian study in 2002 showed that patients who responded to intrathecal drug treatment for failed low back syndrome is cost-effective in the long term, despite high initial costs of the implantable devices.
Conclusion

In this chapter, we described the most common modalities of management. However, there is no single approach that covers every patient. Further, typical patients present with multiple problems. Thus, this should not be construed as the entire evaluation. Only relevant descriptions are provided. Abuse and overuse of multiple procedures is a major concern. These guidelines must not be used to justify multiple procedures, without documentation of medical necessity.
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LOW BACK PAIN AS PERCEIVED BY THE PAIN SPECIALIST


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MITOCHONDRIAL DISORDERS

- A Review of Anesthetic Considerations -

HERODOTOS ELLINAS* AND ELIZABETH A.M. FROST**

Introduction

Mitochondrial disorders are defined as diseases that have a defect in mitochondrial metabolism. The mitochondrion is a group of subcellular organelles with faint, threadlike granules. Mitochondria convert energy from food molecules into adenosine triphosphate (ATP), the main source of energy for most cell functions and manifest through the Kreb’s citric acid cycle, fatty acid oxidation and oxidative phosphorylation (OXPHOS). OXPHOS is the main source for the formation of ATP. The mitochondrion is also involved in iron metabolism (implicated in Friedreich ataxia), amino acid biosynthesis and apoptosis. A subclass of these disorders, mitochondrial myopathies, is thought to be caused by OXPHOS defects.

Epidemiology

Mitochondrial diseases are caused both by mutations, acquired or inherited, within mitochondrial DNA (mtDNA) and genetic inheritance. They may also be the result of acquired mitochondrial dysfunction due to adverse effects of drugs, infections, or other environmental causes. Mitochondrial DNA inheritance behaves differently from autosomal and sexually-linked inheritance. Nuclear DNA has two copies per cell (except for sperm and egg cells), one copy being inherited from the father and the other from the mother. Mitochondrial DNA, however, is strictly inherited from the mother and each mitochondrial organelle typically contains multiple mtDNA copies. During cell division the mitochondrial DNA copies segregate randomly between the two new mitochondria, and then those new mitochondria make more copies. If only a few of the mtDNA copies inherited from the mother are defective, mitochondrial division may cause most of the defective copies to end up in just one of the new mitochondria. Mitochondrial disease may become clinically apparent once the number of affected mitochondria reaches a certain level; this phenomenon is called "threshold expression". To date, more than 200 disease-causing point mutations to the mitochondrial genome have been reported in the Mitomap database (www.mitomap.org).

Although the structure of mtDNA was known over 40 years ago, and the consequences of impairment of the OXYPHOS pathway even earlier, mutations of the mitochondrial genome have been described more recently1,2,3. Although much as been learned over the past 2 decades, about mitochondrial disorders, the relationship between the molecular pathology of mtDNA-related diseases and the varied but often specific phenotypes associated with different mutations remains incompletely understood. The model most frequently

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used to study mitochondrial disease is the syndrome of mitochondrial encephalopathy, lactic acidosis and stroke like symptoms (MELAS) first described 25 years ago. Of the 200 disease causing points in the mitochondrial genome, at least 30 have been associated with MELAS.

It takes about 3000 genes to make a mitochondrion. Mitochondrial DNA encodes just 37 of these genes; the remaining genes are encoded in the cell nucleus and the resultant proteins are transported to the mitochondria. Only about 3% of the genes necessary to make a mitochondrion (100 of the 3000) are involved in the making of ATP. More than 95% (2900 of 3000) are involved with other functions tied to the specialized functions of the differentiated cell in which it resides. These functions change as the body develops from embryo to adult, and tissues grow, mature, and age. These non-ATP-related functions are intimately involved with most of the major metabolic pathways used by a cell to build, break down, and recycle its molecular building blocks. Cells cannot make the RNA and DNA they need to grow and function without mitochondria and the building blocks of purines and pyrimidines. Mitochondria contain the rate-limiting enzymes for pyrimidine biosynthesis (dihydroorotate dehydrogenase) and heme synthesis (d-amino levulinic acid synthetase) required to make hemoglobin. In the liver, mitochondria are specialized to detoxify ammonia in the urea cycle. Mitochondria are also required for cholesterol metabolism, for estrogen and testosterone synthesis, for neurotransmitter metabolism, and for free radical production and detoxification. Enzymes within mitochondria oxidize fat, protein, and carbohydrates to generate ATP via the electron transport chain a process known as oxidative phosphorylation. The mitochondrial complexes (I-V) that are part of this process are multimeric proteins embedded in the inner mitochondrial membrane. Mutations in any of these proteins produce many different clinical manifestations. Although the majority of these proteins are encoded by nuclear DNA thus producing Mendelian autosomal inheritance, some are encoded by mitochondrial DNA and therefore maternal inheritance is seen. The first step of the respiratory chain/OXPHOS process is the conversion of NADH to NAD and it is the most common site of mitochondrial aberrations. Its three major forms include the fatal infantile multisystem disorder, myopathy, and mitochondrial encephalopathy. The latter two forms have variable course and prognosis and other than metabolic supplements and dietary modifications to slow down progression of the disease, multivisceral organ transplantation may be the only available definitive treatment.

**Genocopies of Mitochondrial Disease**

Genocopies are diseases that are caused by the same mutation but which may not look the same clinically. Because mitochondria perform so many different functions at different sites, with mutations and developed abnormalities, hundreds of different mitochondrial diseases may occur. Each disorder produces a spectrum of abnormalities that can make differential diagnosis difficult in the early stages. Because of the complex interplay between the hundreds of genes and cells that must cooperate for metabolic stability, it is a hallmark of mitochondrial diseases that identical mtDNA mutations may not produce identical diseases.

**Phenocopies of Mitochondrial Disease**

The converse is also true: different mutations in mtDNA and nDNA can lead to the same diseases. In genetics, these are known as phenocopies. One example is Leigh syndrome, which can be caused by about a dozen different gene defects. Leigh syndrome, originally a neuropathological description of the brain of one affected child, was described by Leigh, in 1951. It is characterized by bilaterally symmetrical MRI
abnormalities in the brain stem, cerebellum, and basal ganglia, and often accompanied by elevated lactic acid levels in the blood or cerebrospinal fluid. Leigh syndrome may be caused by the NARP mutation, the MERRF mutation, complex I deficiency, cytochrome oxidase (COX) deficiency, pyruvate dehydrogenase (PDH) deficiency, and other unmapped DNA changes. However, not all children with these DNA abnormalities go on to develop Leigh syndrome.

Aging and Other Factors

Mitochondrial diseases are even more complex in adults because detectable changes in mtDNA occur with age and, conversely, the aging process itself may result from deteriorating mitochondrial function. There is a broad spectrum of metabolic, inherited and acquired disorders in adults in which abnormal mitochondrial function has been postulated or demonstrated. Growth retardation is common.

Incidence

The estimated incidence of mitochondrial myopathies is about 1:4,000 but the variable symptomatology makes this number most probably an underestimate. About 1 in 4,000 children in the United States will develop mitochondrial disease by the age of 10 years. Up to 4,000 children per year in the US are born with a type of mitochondrial disease.

Classification

Mitochondrial disorders are divided roughly into ragged-red fiber disorders and non ragged-red fibers ones based on subsarcolemmal accumulations of abnormal mitochondria and their intense red appearance with histologic staining.

Ragged-red fiber disorders include:
1. Kearns-Sayre syndrome.
3. Myoclonic epilepsy with ragged red fibers (MERRF).
5. Pearson syndrome.

Non ragged-red fiber disorders include:
1. Leigh encephalopathy.
2. Neuropathy, Ataxia, Retinitis Pigmentosa (NARP).

A further classification is depicted in Table 1.
Table 1

There are many manifestations of Mitochondrial diseases, seen at different ages

<table>
<thead>
<tr>
<th>MITCHONDRIAL DISORDER</th>
<th>AGE of Dx (years)</th>
<th>MANIFESTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kearns-Sayre Syndrome</td>
<td>&gt;5 &lt;15</td>
<td>progressive external ophthalmoplegia, retinitis pigmentosa, cardiac conduction defect, dilated cardiomyopathy</td>
</tr>
<tr>
<td>MELAS</td>
<td>late childhood, early adulthood</td>
<td>neurological symptoms-strokes, seizures, headaches</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td></td>
<td>cardiac conduction defect, cardiomyopathy</td>
</tr>
<tr>
<td>MERRF</td>
<td>childhood, young adulthood</td>
<td>seizures, progressive mental retardation</td>
</tr>
<tr>
<td>PEO</td>
<td>adulthood</td>
<td>similar to Kearns-Sayre syndrome</td>
</tr>
<tr>
<td>Pearson Syndrome</td>
<td>infancy, early childhood</td>
<td>refractory sideroblastic anemia, usually fatal</td>
</tr>
<tr>
<td>Leigh encephalopathy</td>
<td>perinatal time, early infancy</td>
<td>diffuse encephalopathy, dysphagia, hypotonia, central respiratory insufficiency</td>
</tr>
<tr>
<td>NARP</td>
<td>young adulthood</td>
<td>Weakness, ataxia, retinopathy, learning disability</td>
</tr>
</tbody>
</table>

Other diseases associated with mitochondrial dysfunction include:

- Diabetes mellitus and deafness (DAD)
  - this combination at an early age can be due to mitochondrial disease
- Leber's hereditary optic neuropathy (LHON)
  - visual loss beginning in young adulthood, characterized by progressive loss of central vision due to degeneration of the optic nerves and retina
- Wolff Parkinson White syndrome
- Multiple sclerosis type disease
- Myoneurogenic gastrointestinal encephalopathy (MNGIE)
  - gastrointestinal pseudo-obstruction
  - neuropathy

Conditions such as Friedreich's ataxia can affect the mitochondria, but are not associated with mitochondrial proteins. Deficiencies of each of the respiratory chain complexes can result in separate conditions such as Complex I (NADH-CoQ reductase) deficiency. Deficiencies of these complexes both individually and in combination have been associated with the aforementioned ragged-red and non ragged-red fiber disorders.

Clinical Presentation
Because of the numerous mutations, these disorders may present with a variety of symptoms and at a different age\(^8,9\). As a rule of thumb, progressive muscle weakness and exercise intolerance are the main symptoms. Although weakness of the muscles controlling the eyes and eyelids can be a prominent feature in some patients, in others, weakness of the muscles of the face and neck with subsequent difficulty in speech and in swallowing can be the clinical manifestation. The degree of exercise intolerance varies with each individual; in some, problems with walking are the issue, in others jogging or more intense activities increase the severity of symptoms. Muscle pain and muscle injury can result in rhabdomyolysis and myoglobinuria with end result of renal insufficiency and failure.

Since deficiency in ATP production is the end result of these disorders, organs with high energy demands such as the brain, the heart and the kidneys may be involved early. Headaches, hearing deficits, seizures and learning disabilities with mental retardation can be the cerebral manifestations of ATP insufficiency (stroke-like episodes in MELAS). Cardiac conduction abnormalities requiring pacemaker placement and cardiac muscle damage with cardiomyopathy are common concerns in the cardiovascular system.

Other systems affected include the respiratory system with shortness of breath and insufficiency requiring ventilator support, the gastrointestinal system with symptoms such as unexplained vomiting and dysphagia and the endocrine system with diabetes and exocrine pancreatic insufficiency.

**Diagnosis**

MitoD involve multiple systems and are usually progressive. Along with history and physical, complete neurological examination and follow up is warranted. Laboratory testing should include basic and specialized testing such as lactate, pyruvate, creatinine phosphokinase (CPK), plasma amino acid levels and urine for organic acids (Table 2). Although abnormal test results may support the diagnosis of mitoD, a single normal test cannot rule it out. The triad of lactic acidosis, seizures and stroke-like episodes is central to the diagnosis of MELAS, occurring in >90% of patients\(^10\). Lactic acidosis is determined either from serum or cerebrospinal fluid. Stroke–like episodes stress the non-ischemic origin of these events. Affected areas of the brain have an irregular distribution, consistent with a metabolic or small vessel etiology rather than disease associated with a classical vascular supply. Clinically, patients may have episodes of at least partially reversible aphasia, hemianopsia, and cortical blindness. Initially a mild sensorineural hearing loss is common. Migraine is also a common feature. An especially common systemic manifestation is diabetes mellitus, described in the earliest reports of mitochondrial disease\(^4\). There appears to be a firm association between MELAS, the m.3243A>G mutation and non insulin dependent diabetes.

**Table 2**

*Some of the common preoperative tests that should be performed in patients with mitochondrial disorders*
LABORATORY EVALUATION

Complete Blood Count (CBC)  
Electrolytes and Glucose  
Creatinine  
Liver tests and ammonia  
Coagulation parameters  
Creatinine phosphokinase (CPK)  
Plasma lactate and pyruvate levels  
Plasma amino acids  
Urine organic acids  
Plasma acylcarnitine analysis

Despite the episodic nature, MELAS as with the other mitochondrial diseases, is progressive leading to dementia and severe neurologic deficits.

Brain imaging, audiology testing, ophthalmologic exam and electroencephalogram may identify central nervous system involvement whereas electrocardiogram and echocardiogram can detect cardiac disease\(^\text{11}\).

Skin or skeletal muscle biopsies can provide invaluable information but again they are not 100% sensitive. Fresh muscle biopsy may provide better results but not only can it be very expensive (up to $10,000 for a complete analysis) but it is also performed in only a few centers in North America making it difficult for patients to access.

Karyotyping and genetics consultation may benefit evaluation of patients with developmental and learning disabilities.

**Malignant Hyperthermia**

The only known myopathy disorders with true association with MH and the need for non-triggering anesthesia are:

1. Central Core disease  
2. King-Denborough syndrome and  
3. Evans myopathy

Although for the undiagnosed myopathic patient, a non-triggering technique should be employed, the estimated risk of malignant hyperthermia (MH) or rhabdomyolysis based on record review in a population of children with suspected neuromuscular dystrophy is less than 1%.

Two earlier reports of MH in association with mitoD have been recorded but most recent anesthesia reviews suggest that non-triggering anesthetics are not essential for the management of these disorders\(^\text{12,13}\). A wide range of anesthetics has been used including general anesthesia with volatile anesthetics, intravenous...
anesthesia or regional block with local anesthetics. Mitochondrial disorders, especially MELAS, are now considered to have separate pathologies from MH.

**Treatment**

Therapeutic options for patients with mitochondrial diseases remain limited. A recent trial of the role of dichloroacetate was terminated due to peripheral toxicity. There are no curative therapies at present. Symptomatic management addressing cardiac, renal, growth, and nutritional issues are emphasized. Other treatments are based on the use of antioxidants, respiratory chain substrates, and co-factors in the form of vitamins. No consistent benefits have been observed. However, recent studies of a therapeutic role for L-arginine have been promising. Dysfunction in COX activity and its effect on nitric oxide levels may cause the angiopathy and stroke-like episodes and L-arginine may affect the uptake of glutamate and the release of GABA, increasing the production of ornithine. Individual case reports and a prospective trial of L-arginine given orally over 2 years, significantly improved endothelial function. Although many neurologists recommend nutritional supplements (vitamins and anti-oxidants), there is little data of their effectiveness other than Coenzyme Q supplementation. Most patients though, may have already been placed on such additives like carnitine infusion, TPN or simply high dextrose infusions, all of which should be continued intraoperatively to avoid a metabolic crisis.

**Anesthetic Considerations**

The perioperative period carries several challenges for the anesthesiologist. Preoperatively, history, physical, and laboratory/special testing evaluation should be performed early enough for intervention as indicated. Electrolyte correction, especially that of acid-base balance may be necessary and coagulation parameters optimized. Hyperglycemia should be normalized. A specific neurologic finding may require attention or a cardiac conduction abnormality or cardiomyopathy monitored. Fasting guidelines indicate a minimum of 6-8 hours of solid meal avoidance and minimum of 2 hours for clear liquids. These patients not only are at higher risk for aspiration because of their bulbar muscle weakness and gut dysmotility, but they are also in danger of a metabolic crisis with prolonged fasting and inadequate glucose balance. Therefore, a well thought out plan for their IV management should be in place. Avoidance of lactated Ringer’s solution is also recommended to prevent additional lactate load.

A systematic review must be carried out as follows:

**Neurologic**

As noted above, vision, hearing, and speech may be impaired. Cognitive dysfunction is common, including language and memory difficulties. The ability to give informed consent may be impaired. Peripheral neuropathies are common.

**Cardiac Manifestations**
Cardiac muscle has high-energy requirements and thus cardiac disease is common. Cardiomyopathies (especially in children where they may present as the sole anomaly) and congestive cardiac failure should be evaluated and treated. Conduction defects such as Wolff Parkinson White syndrome should be documented. Bundle branch blocks and infranodal conduction defects are not uncommon and appropriate cardiac consultation should be sought.

**Pulmonary Changes**

Intrinsic pulmonary disease is rare. Pulmonary artery hypertension has been reported and associated with serum and cerebrospinal fluid acidosis. Muscle biopsy in this case revealed cytochrome c oxidase-positive ragged red fibers and molecular testing demonstrated the presence of the m.3243A>G mutation.

**Renal Abnormalities**

Renal disease occurs less commonly than cardiac or endocrine problems but may manifest as de Toni-Debre-Fanconi syndrome, nephrotic proteinuria or focal segmental glomerulosclerosis. Bartter-loke syndrome, hypercalciuria and tubulointerstitial nephritis have also been reported.

**Gastrointestinal Involvement**

Several features have been described associated with mitochondrial diseases including constipation, gastric discomfort, hepatic pathology, pancreatitis, gastroparesis, intestinal pseudo-obstruction and malabsorption.

**Dermatologic Changes**

Vitiligo, scaly and pruritic rashes with diffuse erythema and reticular pigmentation have all been described. However, skin changes appear to be relatively minor.

**Intraoperative Management:** In addition to standard ASA monitoring, arterial cannulation should be instituted for continuous hemodynamic monitoring as well as for frequent blood sampling for blood gases, electrolytes, blood glucose and lactate monitoring. Normothermia should be the goal to prevent added stress and increase in metabolic demands.

Precautions against aspiration with rapid sequence induction (RSI) and cricoid pressure may be considered in some patients, based on co-morbid conditions and degree of skeletal muscle weakness. Depending on hepatic and renal insufficiency, muscle relaxants should be used cautiously. Although there is paucity of data regarding succinylcholine and mitochondrial disorders, its association with MH in one case report and possible hyperkalemic response should be considered.

Volatile anesthetics have been used in mitoD without complications but they have been shown to impair OXPHOS by inhibition of complex I. This in turn can impair CNS metabolism and cause cardiac dysfunction leading to a potential increase in sensitivity to these agents.
Total intravenous anesthesia has been advocated by many as a safer, non-triggering anesthetic technique\textsuperscript{19}. The safety of propofol has been questioned because of its lipid component possibly affecting fatty acid oxidation and because of a direct effect on the mitochondrial respiratory chain\textsuperscript{23,24}. Both of these effects may predispose patients to a propofol infusion-like syndrome. This syndrome is characterized by lactic acidosis, bradycardia, rhabdomyolysis, cardiac and renal failure and although diagnosed mainly with longer duration infusions (>48hrs), in susceptible patients even short-term infusions can cause symptoms. Ketamine has not been implicated as a deleterious agent in mitoD and its analgesic properties can be an adjunct to the overall anesthetic management.

Regional anesthesia may be an attractive alternative for mitoD patients but local anesthetics have been shown to impair OXPHOS as well and may lead to inefficient ATP synthesis. Clinically, regional anesthesia has been used successfully and supporters indicate that its use may allow a decrease in opioids and thus a lower risk of respiratory depression with worsening acidosis. Also if a regional technique is used alone, volatile anesthetic sensitivity would be avoided.

\textbf{Postoperatively} minimizing metabolic stress and avoidance of increases in metabolic demand should be the ultimate goal including avoiding shivering, providing adequate analgesia, maintaining normoglycemia and a normal respiratory status. Even with a diligent perioperative plan, mitoD patients may require close monitoring in an intensive care setting.

\textbf{Conclusion}

Although uncommon, mitoD can pose many challenges for the anesthesiologist. There is no “safest” anesthetic technique; the choice of anesthetic should be individualized to the patient’s needs. Consultation with experts in the field and the subspecialists in a multidisciplinary approach can provide excellent assistance with co-morbid issues and allow for good prognosis even in complex patients with multiorgan disease.
References

MUCOPOLYSACCHARIDOSES: ANESTHETIC CONSIDERATIONS AND CLINICAL MANIFESTATIONS

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Abstract

Mucopolysaccharidosis (MPS) is a group of genetic disorders that present challenges during anesthetic care and in particular difficulty with airway management. Patients should be managed by experienced anesthesiologists at centers that are familiar with these types of conditions. Rarely encountered disease states have been identified as important topics in the continuing education of clinical anesthesiologists. This review will define MPS, describe the pathophysiology of MPS, describe how patients with this rare lysosomal storage disorders have dysfunction of tissues, cite the incidence of MPS, list the clinical manifestations and specific problems associated with the administration of anesthesia to patients with MPS, present treatment options for patients with MPS, define appropriate preoperative evaluation and perioperative management of these patients, including, to anticipate potential postoperative airway problems.

Introduction

Mucopolysaccharidoses (MPS) are a group of rare genetic lysosomal storage disorders characterized by the deficiency in or complete lack of necessary lysosomal enzymes required for the stepwise breakdown of glycosaminoglycans (GAGs, also known as mucopolysaccharidoses)1-5. Consequently, fragments of GAGs accumulate intracellularly in the lysosome resulting in cellular enlargement causing disruption/dysfunction of structure and function of tissues. This process leads to numerous clinical abnormalities. Incidence of all types of MPS is reported to be between 1 in 10,000 to 1 in 30,000 live births and are transmitted autosomal recessive except for MPS II which is X-linked14.

Pathophysiology

Glycosaminoglycans are long-chain complex carbohydrates consisting of repeating sulfated acidic and amino sugar disaccharide units. They are usually linked to proteins to form proteoglycans, which are the major

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constituents of the ground substance of connective tissue, lubricant in joint fluid, and the surface coating that initially binds growth factors to cells. The major GAGs are chondroitin-4-sulfate, chondroitin-6-sulfate, heparan sulfate, dermatan sulfate, keratan sulfate, and hyaluronic acid. In the organism, these substances are degraded by the sequential action of lysosomal enzymes leading to a stepwise shortening of the terminal sulfate, acidic, and amino sugar residues. Deficient/dysfunctional activity of the degradative enzymes results in MPS disorder of which there are eleven types based on levels of severity. The clinical phenotype of the disorder depends upon the distribution and turnover of the substrate affected by the deficiency, rather than the distribution of the enzyme.

**Classification**

Of the 11 total MPS disorders, there are 7 major types classified I through IX. MPS V, formerly Scheie syndrome, and MPS VIII are no longer recognized. The MPS disorders are differentiated by clinical features and age at presentation and biochemically by the associated enzyme deficiency. As a general rule, the impaired degradation of heparan sulfate is more closely associated with mental deficiency, and the impaired degradation of dermatan, chondroitin and keratan sulfate results in mesenchymal abnormalities. Overall, these disorders can be grouped into four broad categories according to their dominant clinical features:

1. Soft tissue storage and skeletal disease with or without brain disease (MPS I, II, VII).
2. Soft tissue and skeletal disease (MPS VI).
3. Primarily skeletal disease (MPS IVa, IVb).
4. Primarily CNS disease (MPS IIIa-d).

**Table 1**

<table>
<thead>
<tr>
<th>Number</th>
<th>Eponym</th>
<th>Enzyme deficiency</th>
<th>GAG stored</th>
<th>Craniofacial abnormalities</th>
<th>Joint and skeletal deformities</th>
<th>Cardiac involvement</th>
<th>Visceral, visual, and neurologic manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS I (severe)</td>
<td>Hurler syndrome</td>
<td>α-L-iduronidase</td>
<td>dermatan sulfate, heparan sulfate</td>
<td>macrocephaly, coarse facies, macroglossia, hydrocephalus</td>
<td>stiff joints, thoracolumbar kyphosis, possible odontoid deformity, short neck, short stature</td>
<td>coronary intimal and valvular thickening, mitral regurgitation, aortic regurgitation, cardiomegaly</td>
<td>hepato-splenomegaly; umbilical and inguinal hernias; corneal clouding; severe mental retardation</td>
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<tr>
<td>MPS I (attenuated)</td>
<td>Scheie syndrome</td>
<td>α-L-iduronidase</td>
<td>dermatan sulfate, heparan sulfate</td>
<td>coarse facies, macroglossia, prognathia</td>
<td>short neck, normal stature</td>
<td>aortic regurgitation</td>
<td>hepato-splenomegaly; umbilical and inguinal hernias; corneal clouding</td>
</tr>
<tr>
<td>MPS I (attenuated with different features)</td>
<td>Hurler-Scheie syndrome</td>
<td>α-L-iduronidase</td>
<td>dermatan sulfate, heparan sulfate</td>
<td>macrocephaly, coarse facies, macroglossia, micrognathia</td>
<td>diffuse joint limitation, short neck, short stature</td>
<td>mitral and aortic valve thickening and regurgitation</td>
<td>Hepatosplenomegaly, umbilical and inguinal hernias, corneal clouding</td>
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<td>MPS II (severe)</td>
<td>Hunter syndrome (severe)</td>
<td>iduronate sulfatase</td>
<td>dermatan sulfate, heparan sulfate</td>
<td>Macrocephaly, coarse facies, hydrocephalus</td>
<td>diffuse joint limitation, short neck, short stature</td>
<td>coronary intimal thickening, ischemic cardiomyopathy</td>
<td>Hepatosplenomegaly, no corneal clouding</td>
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<tr>
<td>MPS II (attenuated)</td>
<td>Hunter syndrome (mild)</td>
<td>iduronate sulfatase</td>
<td>dermatan sulfate, heparan sulfate</td>
<td>coarse facies, mild stiff joints, short stature, dysphagia</td>
<td>minimal to none</td>
<td>severe retardation, behavioral problems, diarrhea</td>
<td></td>
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<tr>
<td>MPS IIIA (symptoms appear after the first year of life)</td>
<td>Sanfilippo A syndrome</td>
<td>Heparan sulfatase</td>
<td>heparan sulfate</td>
<td>coarse facies, heavy eyebrows that meet in center of face above the nose</td>
<td>minimal to none</td>
<td>developmental delay, behavioral problems</td>
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<td>MPS IIIB</td>
<td>Sanfilippo B syndrome</td>
<td>β-N-acetylglucosaminidase</td>
<td>heparan sulfate</td>
<td>coarse facies</td>
<td>minimal to none</td>
<td>developmental delay, behavioral problems</td>
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<tr>
<td>MPS IIIC</td>
<td>Sanfilippo C syndrome</td>
<td>β-glucosaminidase acetyltransferase</td>
<td>heparan sulfate</td>
<td>coarse facies</td>
<td>minimal to none</td>
<td>developmental delay, behavioral problems</td>
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<tr>
<td>MPS IIID</td>
<td>Sanfilippo D syndrome</td>
<td>N-acetylglucosamine 6 sulfatase</td>
<td>heparan sulfate</td>
<td>coarse facies</td>
<td>minimal to none</td>
<td>developmental delay, behavioral problems</td>
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<tr>
<td>MPS IVA</td>
<td>Morquio syndrome, type A</td>
<td>galactose sulfatase</td>
<td>keratan sulfate, chondroitin-6-sulfate</td>
<td>coarse facies</td>
<td>joint laxity, severe kyphoscoliosis, odontoid hypoplasia, short neck, C1-C2, C2-C3 subluxation, short stature</td>
<td>aortic regurgitation</td>
<td>mild corneal opacities, hepatosplenomegaly</td>
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<tr>
<td>MPS IVB</td>
<td>Morquio syndrome, type B</td>
<td>beta galactosidase</td>
<td>Keratan sulfate, chondroitin-6-sulfate</td>
<td>coarse facies</td>
<td>joint laxity, severe kyphoscoliosis, odontoid hypoplasia, short neck, C1-C2, C2-C3 subluxation, short stature</td>
<td>aortic regurgitation</td>
<td>mild corneal opacities, hepatosplenomegaly</td>
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</table>
Clinical Manifestations

As mentioned previously, MPS disorders are characterized by progressive craniofacial, joint, and skeletal deformities, progressive cardiac involvement, and early death from pulmonary infection or cardiac failure often before childhood\textsuperscript{1-18}. Hurler syndrome is the prototypical MPS and occurs in 1 in 100,000 live births (Fig. 1)\textsuperscript{13,14}. GAGs deposits lead to thickened heart valves, and valvular insufficiency more often than stenosis. Myocardial hypertrophy, ventricular dysfunction and cardiomyopathy result from accumulation of GAGs in the myocardium and frequently cause congestive heart failure and death. Intimal deposition of GAGs causes coronary luminal narrowing and occlusion that can be progressive\textsuperscript{1-16}, GAGs are also deposited in abdominal viscera leading to hepatosplenomegaly (HSM) in most if not all patients. Umbilical and inguinal hernias can be due to abdominal protuberance from hepatosplenomegaly. HSM and ineffective connective tissue support of the anterior abdominal wall often occurs. In addition to heart disease and HSM, most infants have chronic pulmonary disease caused by the thoracic cage restriction due to kyphoscoliosis, airway obstruction secondary to deposition of GAGs into the upper airway structures, recurrent pulmonary infection, pulmonary hypertension, and cardiomyopathy. Tongue protrusion and excessive tracheobronchial secretions are common\textsuperscript{4-22}.

\textit{Fig. 1}

\textit{Patient with Hurler Syndrome, note his coarse facial features, crouched stance, thickened digits, and protuberant abdomen. This figure was taken from the following internet site: http://medgen.genetics.utah.edu/photographs/pages/hurler syndrome.htm}
Diagnosis

A physician should be suspicious for MPS when a child presents with coarse facies, HSM, bone disease, and heart disease with or without CNS abnormalities. However, the initial presentation may be subtle and signs may be variable, depending on the type and severity of MPS. Measuring urinary GAG concentration can assist in identification of MPS but definitive diagnosis is made by assay of enzyme activity from peripheral blood leukocytes. Additionally, skeletal radiographs may reveal the characteristic pattern of skeletal abnormalities known as dysostosis multiplex. An eye examination should be performed to assess corneal clouding and glaucoma which is most common in MPS I, II, VI and VII. A cardiac evaluation should be completed to adequately assess valvular and myocardial disease. A comprehensive neurologic examination estimates the potential for spinal cord compression and hydrocephalus.

Complications

Cardiopulmonary complications in patients with MPS are the most common cause of death. Respiratory abnormalities are the result of airway obstruction, neurologic compromise, recurrent infections, skeletal restrictions, and/or organomegaly, all of which can lead to pulmonary insufficiency, severe
sleep apnea and sudden death from central apnea. MPS IV patients are especially prone to high cord compression secondary to atlantoaxial instability and odontoid dysplasia, which can lead to depressed respiration or sudden respiratory arrest. Cervical fusion is recommended. As previously stated, upper airway obstruction is also a cause of respiratory compromise. This obstruction can be due to redundant airway tissue caused by MPS deposition in the soft tissues of the nasopharynx. There may be enlarged tonsils and adenoidal tissue along with macroglossia and thickened gums. Secretions are excessive due to chronic or recurrent ear and sinus infections. Treatment focuses on maintenance of a stable airway. Obstruction can be temporarily reduced with removal of tonsils and adenoids along with the use of positive airway pressure.\textsuperscript{13,19}

Cardiac abnormalities are well documented. Valvular disease is caused by progressive thickening of the mitral and aortic valves and leads to insufficiency more often than stenosis. It is common in MPS I, II, VI. The defect typically results in heart failure and those severely affected may require valve replacement. Coronary vessel narrowing secondary to intimal deposition of MPS develops and impairs coronary vessel flow. Cardiac ischemia results. Pulmonary hypertension may exacerbate right heart failure.\textsuperscript{16,19}

Skeletal and connective tissue complications develop as GAG’s accumulate in bones, joints, and ligaments. Dysostosis multiplex and odontoid hypoplasia are known to affect patients with MPS I, II, VI, VII and MPS I, IV and VII respectively. Hypoplasia can lead to atlantoaxial instability, C1-C2 subluxation, and high spinal cord compression. Measures for prophylactic cervical fusion should be undertaken to prevent progressive cord compression. Patients also suffer from vertebral subluxation and kyphoscoliosis throughout the spinal column which can compromise the spinal cord and may need spinal fusion for stabilization. Unfortunately, patients typically heal poorly from such surgeries and often have complications requiring repeat surgery. Short stature is also a common finding throughout the spectrum of MPS types. Very often, patients present with joint stiffness, secondary to accumulation of MPS in the synovial fluid and other connective tissues of the joints.\textsuperscript{24-28}

Gastrointestinal complications include recurring inguinal and umbilical hernias and hepatosplenomegaly with increased intrabdominal pressure. Surgical repair is often performed and may have to be repeated.\textsuperscript{13,16,19}

Neurological complications are well documented. Developmental delay and progressive neurologic decline occur in the severe form of MPS I, II, III, V, and VII. Communicating hydrocephalus frequently develops in MPS I, II, III, VI, and VII due to the engorgement of arachnoid granulations by storage material, impeding resorption of cerebrospinal fluid and increasing intracranial pressure. In MPS III, hydrocephalus is secondary to ventricular enlargement due to cerebral atrophy in the later stages of the illness. Pachymeningitis cervicalis, a progressive thickening and scarring of the meninges around the cervical spinal cord caused by accumulation of MPS, is another neurologic complication. This thickening may form a sleeve around the spinal cord that impedes the flow of cerebrospinal fluid (CSF) and progressively compresses the cervical cord. Cord compression from pachymeningitis cervicalis and odontoid dysplasia can result in progressive ascending paresis and paralysis.\textsuperscript{13,18}

Ophthalmic and auditory complications are common. Ophthalmologic manifestations include corneal clouding and potentially blindness may develop. Eye examinations should be performed at the time of diagnosis and annually thereafter.\textsuperscript{29,30} Auditory manifestations include conductive and neurosensory deafness. Hearing loss may be attributable to frequent ear infections, defective ossification in the middle ear, scarring of the tympanic membrane, or nerve damage. Annual audiologic exams are warranted and are particularly important for patients with MPS I. Hearing aids are beneficial.\textsuperscript{31,32}
Therapy

Treatment for MPS disorders is usually symptomatic and not specific. Bone marrow transplantation (BMT) has been used to successfully treat some of the disorders in the spectrum of MPS. In most patients with successful engraftment, transplantation reduces hepatosplenomegaly, increases joint mobility, decreases airway obstruction, improves cardiac function, decreases CSF pressure, and especially in younger patients, may stabilize mental regression. Unfortunately, BMT does not correct skeletal disorders nor prevent CNS decline in severe cases. Immunosuppressant treatment is required. The therapy is routinely offered only to MPS patients with Hurler syndrome under approximately two years of age. It is less commonly used in mild MPS II, VI, and VII. Cord blood transplantation is another potential source for transplantation.

Emerging treatments for MPS beyond BMT include enzyme replacement therapy (ERT), substrate reduction therapy (SRT), chaperone-mediated therapy, and gene therapy. Although complete clinical efficacy has not yet been completely seen for any of these therapies, it appears that future developments will lead to a disease-modifying treatment. Enzyme replacement therapy with recombinant iduronate-2-sulphatase (idursulfase) is being clinically investigated and weekly intravenous infusions of idursulfase improve many of the symptoms and signs of MPS.

Anesthesia Considerations

Preoperative evaluation

Considerations include assessment of neurologic function, anticipation of a difficult airway and ventilatory management, cardiac complications, skeletal disease, and visceral manifestations. Chest x-ray, arterial blood gas analysis and pulmonary functions tests may be indicated in patients with chronic pulmonary infections and/or kyphoscoliosis. Vital capacity, functional residual capacity, and total lung capacity are often reduced by skeletal restrictions. Preoperatively, the goal should be to optimize lung capacity and may include physiotherapy, pulmonary toilet, and/or antibiotics if infection is present. To assess clinically relevant spinal disease, radiographs should be performed to identify atlantoaxial subluxation, especially in patients with Morquio and Hurler syndromes. Flexion-extension cervical films may confirm the potential for subluxation and demonstrate tracheal collapse on flexion. Atlantoaxial subluxation contraindicates cervical extension during endotracheal intubation. Spinal cord compression due to subluxation frequently occurs within the spectrum of MPS. Patients presenting with clinical manifestations such as abnormal gait, sensory changes, or weakness in lower extremities should be evaluated by a neurologist. Somatosensory evoked potentials can be used to detect early cord compression and guide the timing of surgical intervention. Patients with MPS I who undergo spinal surgery are at increased risk of major complications, including spinal cord infarction and spinal instability. Communicating hydrocephalus can be seen, and if suspected, measurement of CSF pressure should be considered. With increased ICP, ventriculostomy may successfully reduce CSF pressure but typically does not reverse clinical disease significantly. An enlarged heart and pulmonary congestion should prompt evaluation by 2D echocardiography, which can detect right ventricular hypertrophy with strain, conduction blocks, left atrial enlargement, tachydysrhythmias, and ischemic changes. Systolic murmurs are common and this too should prompt evaluation by echocardiography. If patients experience chest pain or clinical symptoms...
that suggest ischemia, more invasive diagnostic tests are indicated such as angiography. Case reports have suggested that the contribution of cardiac involvement, particularly mitral insufficiency and cardiomegaly, in stress tolerance related to anesthetic management was minimal; however, a few instances have pointed to severe and extensive coronary obstruction as a cause for two intra-operative deaths. Patients with moderate/severe skeletal disease should have ongoing monitoring by an orthopedic surgeon. Spine deformities may require fusion; acetabular hip dysplasia can be managed with osteotomy and genu valgum with epiphyseal stapling. Carpal tunnel release can provide relief and the return of some hand function. Visceral manifestations are common. Inguinal hernias are commonly repaired before disease diagnosis. Umbilical hernias often recur, due probably to hepatosplenomegaly. Since the most common clinical manifestations include chronic upper respiratory infections, it is important to identify any potential infectious processes. Tonsillectomy and adenoidectomy should be considered for all patients who develop airway compromise. For patients with MPS, they are typically evaluated for routine ear, nose, and throat exams annually; however, careful preanesthetic assessment may be invaluable if underlying pathophysiological process are subclinical and have not been identified.

**Anesthesia Drug Considerations**

Premedication sedation should be used cautiously if at all because of the risks of upper airway obstruction, respiratory depression, hypercarbia, and cardiorespiratory arrest. Opioids should be avoided if airway problems are anticipated because of respiratory depression. Oropharyngeal secretions can be controlled be anticholinergics, such as scopolamine or glycopyrrolate. Hurler syndrome being the prototypical form and most severe disorder has an incidence of difficult tracheal intubation as high as 50%. Some authors suggest intravenous induction for younger patients with lesser degrees of craniofacial involvement and inhaled inductions in older patients with established or anticipated airway difficulties. Others maintain that inhalation induction is preferable; however, intravenous induction may be necessary for the severely retarded and uncooperative patient. Many authors suggest induction with intramuscular ketamine over inhalation induction.

MPS patients seem not to be at increased risk for malignant hyperthermia. Maintenance anesthesia is usually with an inhalational agent. The muscle relaxant of choice is often a short acting non-depolarizing muscle relaxant.

**Airway Management**

Patients with MPS may be difficult to ventilate secondary to abnormal facies. An air-cushioned pediatric face-mask may be applied upside down, with the broad chin edge of the mask over the patient’s brow and nose and the narrow nasal bridge of the mask over the open mouth and protruding tongue. Advanced airway management instruments should be available including an assortment of face masks, endotracheal tubes, laryngoscope blades and handles, fiberoptic equipment, Glidescope®, the difficult airway cart, and even a surgeon standing by ready to do an emergency tracheostomy. Direct laryngoscopy for awake orotracheal intubation will be difficult. Airway manipulation is much easier to perform in deeply sedated spontaneously ventilating patients. As mentioned above, atlantoaxial subluxation secondary to odontoid hypoplasia/dysplasia with spinal cord and brainstem compression may occur during cervical hyperextension. Cervical traction can
be used to prevent manipulation of the neck. Since deposits make it extremely difficult to feel the trachea, utilization of retrograde catheter-guided tracheal intubation is not recommended. Blind nasotracheal intubation and tracheostomy carry significant risks and are recommended only in emergency situations. Some authors believe that fiberoptic bronchoscope should be available for all known difficult intubations presenting for anesthetic management.\textsuperscript{13}

**Postoperative Management**

The emerging child may experience difficulty breathing against the high airway resistance of an endotracheal tube. Pulmonary hypertension can be exacerbated and negative pressure pulmonary edema may ensue and require immediate management including mechanical ventilatory support. Multiple attempts at intubation should be avoided because they can lead to symptomatic glottic and subglottic edema. Such iatrogenic conditions are very difficult to treat due to the progressive narrowing of the tracheal lumen by MPS deposits.\textsuperscript{10,13} Utilizing a fiberoptic intubation and then leaving the endotracheal tube in place immediately postoperatively, minimizes airway complications, in particular for those patients who do not meet all the extubation criteria. After tracheal extubation, humidified O2, chest physiotherapy, and postural drainage should be instituted and continued until the patient is ambulatory and able to expectorate excessive secretions.\textsuperscript{10,13}

**Conclusions**

Patients presenting with MPS are often difficult to manage peri-operatively and though new treatments are providing hope, many challenges remain. Understanding the pathophysiology of this group of diseases increases awareness of the potential risks of anesthesia and surgery. Ideally, children with MPS should be managed by anesthesiologists familiar with the disease process to minimize complications and reduce morbidity and mortality.
References


CONTEMPORARY ANESTHESIA MANAGEMENT FOR LIVER TRANSPLANTATION

A Comparison of American and European Methods

DMITRI BEZINOVER*, ZAKIYAH KADRY** AND PIOTR JANICKI***

Abstract

This review article compares the organization of liver transplantation programs, anesthesia management and postoperative care in the United States and Europe.

Liver transplantation is a definitive treatment for end-stage liver disease. The procedure is extremely complex and requires excellent surgical technique and experienced anesthesiologists who are able to provide precise management. Liver transplantation programs, which first started in the United States and a few years later in Europe, have quickly been able to achieve remarkable results.

In the United States one organization, the United Network for Organ Sharing (UNOS) is responsible for the allocation of organs and data collection; in Europe there are various organizations with different levels of cooperation. The major difference between anesthesia management in the United States and Europe is the number of medications available for coagulation improvement. Substances such as prothrombin complex concentrate, fibrinogen, and antithrombin III allow for a greater flexibility in European anesthesia management. Thromboelastography, which is routinely used in the United States for overseeing coagulation, is now increasingly being used in Europe, and seems to be highly effective in providing precise information about coagulation. The overall ICU stay in Europe is longer than in the United States, and services such as maintenance of critical care, immunosuppression and nutrition are not separated in Europe.

Despite these differences in liver transplantation programs, overall one-year patient survival rate is similar in the United States and in Europe, exceeding 85% in both.

A brief history of liver transplantation

The history of solid organ transplantation started in 1954 in the United States with the first successful live-donor related kidney transplant. Dr. Joseph Murray performed the surgery at Brigham Hospital in Boston. The first liver transplant was done nine years later, again in the United States, on 1 March 1963 by Dr. Thomas

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Starzl in Denver, Colorado. Unfortunately, the patient (a 3-year-old child with biliary atresia) died a few hours after the procedure. By 1967, however, Dr. Starzl was successful in achieving long-term survival; an 18-month-old patient was alive one year after transplantation, which was unprecedented. The first European orthotopic liver transplantation was performed by Dr. Roy Calne in 1968 in the U.K., followed by Dr. Alfred Gütgemann, the head of the surgery department at the University of Bonn in 1969. About 40 doctors and nurses participated in the surgery, which lasted 5½ hours and was very successful. The patient survived seven months after the procedure, which was a very good result at the time. In 1972, Dr. Rudolf Pichlmayer, from Hannover, Germany, founded one of the biggest liver transplantation centers in Europe. Since then several transplantation programs have been established in various European countries, especially in Germany, France, England, Spain and Italy, where a large number of transplantations have been performed in different centers. The initial one-year survival rate of 24-30% was drastically improved to 70% in the 1980s, when the effectiveness of cyclosporine was confirmed for organ grafting. The shortage of donor livers forced the development of alternative procedures, such as partial liver transplantation. The first split liver transplants were performed at the same time in the United States and Europe in 1988. In 1989 the first live-donor related liver transplantation was completed by Dr. Russell Strong in Australia.

The competition between the United States and the European Union is ongoing, with the number of transplantations being similar, averaging about 5000-6000 per year (Table 1).

<table>
<thead>
<tr>
<th>To Date</th>
<th>Overall liver transplantation in the United States</th>
<th>Overall liver transplantation in Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988</td>
<td>1713</td>
<td>1280</td>
</tr>
<tr>
<td>1989</td>
<td>2201</td>
<td>1720</td>
</tr>
<tr>
<td>1990</td>
<td>2690</td>
<td>2111</td>
</tr>
<tr>
<td>1991</td>
<td>2953</td>
<td>2508</td>
</tr>
<tr>
<td>1992</td>
<td>3064</td>
<td>2762</td>
</tr>
<tr>
<td>1993</td>
<td>3440</td>
<td>3000</td>
</tr>
<tr>
<td>1994</td>
<td>3652</td>
<td>3330</td>
</tr>
<tr>
<td>1995</td>
<td>3934</td>
<td>3629</td>
</tr>
<tr>
<td>1996</td>
<td>4084</td>
<td>3757</td>
</tr>
<tr>
<td>1997</td>
<td>4188</td>
<td>4038</td>
</tr>
<tr>
<td>1998</td>
<td>4516</td>
<td>4266</td>
</tr>
<tr>
<td>1999</td>
<td>4751</td>
<td>4587</td>
</tr>
<tr>
<td>2000</td>
<td>4997</td>
<td>4821</td>
</tr>
<tr>
<td>2001</td>
<td>5195</td>
<td>4945</td>
</tr>
<tr>
<td>2002</td>
<td>5332</td>
<td>5142</td>
</tr>
<tr>
<td>2003</td>
<td>5673</td>
<td>5095</td>
</tr>
<tr>
<td>2004</td>
<td>6171</td>
<td>5421</td>
</tr>
<tr>
<td>2005</td>
<td>6444</td>
<td>5475</td>
</tr>
<tr>
<td>2006</td>
<td>6651</td>
<td>5487</td>
</tr>
<tr>
<td>2007</td>
<td>6494</td>
<td>5624</td>
</tr>
</tbody>
</table>
Based on OPTN data and ELTR data as of February 4, 2010.

**Organization of the transplantation network**

Soon after the first successful steps in transplantation and the establishment of transplantation centers, it became clear that the procedures had to be coordinated on a regional or national level in order to procure and distribute organs. Gathering transplantation dates and dealing with legal issues became an additional responsibility of these national and international organizations. In the United States, the Southeast Organ Procurement Foundation (SEOPF) was established in 1968 to integrate all transplant programs and to coordinate the research in this field. SEOPF introduced many innovations: in 1977 it initiated the first computer-based organ matching system, and in 1982 it established the kidney center with 24-hour assistance. In 1984 the United Network for Organ Sharing (UNOS) separated from SEOPF and received a federal contract for operating the Organ Procurement and Transplantation Network. Now UNOS operates the computer-based system for organ matching, gathers all information about transplantations, and publishes reports of mortality and survival for all US-active transplant centers. In 2002, UNOS introduced the MELD (Model for End-Stage Liver Disease) scoring system, which changed the organ allocation system in the United States. UNOS was also one of the organizations that took part in the founding of Donate Life America to explain the importance of organ donation to the public. Thanks to UNOS, the idea of organ donation has become more acceptable in all segments of society. Today UNOS coordinates 253 transplant centers with 908 different transplant programs (128 programs for liver transplants, with currently more than 16,000 patients on the waiting list (based on OPTN data 2009). UNOS also provides information about the average waiting time and survival ratio for different organs in different regions.

In Europe, transplant services are organized slightly differently. The structure of transplantation services is more complicated. Depending on the country in Europe, there are several organizations responsible for transplantation.

Founded in 1967 by Dr. Jon J. van Rood, Eurotransplant is the largest organization, with its main office in Holland. The aim of Eurotransplant is similar to that of UNOS: to register all patients who need organ transplants and to improve the matching system. The organization started with the allocation of 11 kidney grafts in the first year and 60 in the following year. About 75 transplantation centers currently participate in Eurotransplant (36 for liver transplantation), and more than 15,000 patients are on the waiting list (about 2500 for liver transplant). The other European national transplantation organizations were founded at about the same time and have the same purpose as Eurotransplant. Balttransplant is the only new organization that has recently been added in order to coordinate transplantation activity in Estonia, Latvia and Lithuania.

The development of liver transplantation programs in Eastern Europe has been relatively slow. In 9 out of 19 former communist countries, early attempts were made to start liver transplantation with very low numbers of procedures and survival rates, below those of the established programs. In the 1980s and 1990s, Hungary, Poland, and in particular the Czech Republic began successful programs with a one-year survival rate of about 90%. In Poland there are currently 5 adult-liver transplantation programs and 1 pediatric liver transplantation program, with about 400 patients on the waiting list and a mean waiting time of 200 days.
In 1985, the European Liver Transplant Registry (ELTR) was founded at the meeting of the European Society for Organ Transplantation in Munich. This step was important for the coordination of procedures, data gathering, and coordinating research between the different transplantation programs in various European countries. Initially, 32 European centers participated in the ELTR. With currently 137 centers from 23 countries, ELTR harbors an enormous scientific potential. ELTR has collected data regarding more than 70,500 transplantations performed in Europe, including data about indications for transplantation, donors’ (including living donors’) and recipients’ blood group compatibility, data about a variety of surgical techniques, mortality reports, graft survival data, data about immunosuppression therapy and recipient survival rates (Table 2 and 3).

### Table 2

**Recipient survival rates in Europe**

<table>
<thead>
<tr>
<th>Year</th>
<th>Survival overall</th>
<th>1 Year Survival %</th>
<th>5 Year Survival %</th>
<th>7 Year Survival %</th>
<th>10 Year Survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985</td>
<td>519</td>
<td>34</td>
<td>22</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>1985-1989</td>
<td>4129</td>
<td>64</td>
<td>53</td>
<td>50</td>
<td>46</td>
</tr>
<tr>
<td>1990-1994</td>
<td>12,007</td>
<td>77</td>
<td>65</td>
<td>61</td>
<td>56</td>
</tr>
<tr>
<td>1995-1999</td>
<td>18.162</td>
<td>82</td>
<td>71</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>2000-2004</td>
<td>22.945</td>
<td>85</td>
<td>74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 2004</td>
<td>18.786</td>
<td>87</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


### Table 3

**Recipient survival rates in the U.S.A**

<table>
<thead>
<tr>
<th>Liver Donor Type</th>
<th>Years Post Transplant</th>
<th>Number of Functioning Grafts</th>
<th>Survival Rate</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cadaveric</td>
<td>1 Year</td>
<td>13,057</td>
<td>86.3</td>
<td>(85.7, 86.8)</td>
</tr>
<tr>
<td>Living</td>
<td>1 Year</td>
<td>823</td>
<td>90.1</td>
<td>(88.1, 92.1)</td>
</tr>
<tr>
<td>Cadaveric</td>
<td>3 Year</td>
<td>12,823</td>
<td>78.0</td>
<td>(77.4, 78.6)</td>
</tr>
<tr>
<td>Living</td>
<td>3 Year</td>
<td>1066</td>
<td>82.7</td>
<td>(80.6, 84.7)</td>
</tr>
<tr>
<td>Cadaveric</td>
<td>5 Year</td>
<td>10,402</td>
<td>72.0</td>
<td>(71.3, 72.7)</td>
</tr>
<tr>
<td>Living</td>
<td>5 Year</td>
<td>505</td>
<td>77.9</td>
<td>(74.7, 81.0)</td>
</tr>
</tbody>
</table>


### Cost Issues

Liver transplantation is one of the most expensive medical procedures performed. It is, therefore, of interest to compare cost variations of liver transplantation between the United States and other countries. The Organization for Economic Cooperation and Development (OECD), which includes 24 European countries, USA, Canada, Japan, Korea, New Zealand and Australia, recently published a report (van der Hilst et al., 2009)
about expenses in this field. The estimated mean cost of a liver transplantation in the United States (in 2005 dollars) was $163,438 ($145,277-$181,598) compared to $103,548 ($85,514-$121,582) for other OECD countries. Patient characteristics, disease characteristics, quality of health care provider, and methodology could not explain this cost difference. Health system characteristics differed between the United States and other OECD countries. Cost differences in liver transplantation between these two groups may be, therefore, largely explained by health system characteristics. It is interesting that within each center the factors having a major influence on cost were: etiology of liver disease, patient status at the time of transplantation, necessity of re-transplantation, and duration of hospital stay. It is unlikely that differences in anesthesia management contribute to the described differences; as based on the United States experience, anesthesia costs are responsible for only a fraction of the total liver transplantation bill. Instead, the higher cost of liver transplantation in the United States is in line with other health costs, including the higher price of hospital stays, physician services, and pharmaceuticals.

**Intraoperative Anesthesia Management**

The general management of anesthesia for liver transplantation is similar in the United States and in Europe. In summary, different transplantation centers have slightly different standards, but overall, general endotracheal anesthesia (GETA) is the standard of care. Epidural anesthesia is not used because of the compromised coagulation and platelet function. Most centers in Europe no longer float a pulmonary catheter (Swan Ganz catheter) in order to monitor cardiac output, pulmonary pressure, and central venous pressure for several reasons: the patient selection process has been improved, the catheters are expensive, and the procedure is invasive and often leads to complications. In the United States, use of the Swan-Ganz (SG) catheter remains relatively common, but there is a clear trend towards a reduction in its use by most centers both in Europe and the United States. Transplant anesthesiologists have instead begun measuring central venous pressure (CVP), as well as using different non-invasive methods for cardiac output estimation and the relay of certain biochemical parameters (e.g., base deficit or lactate level) for volume management during the liver transplantation. In both the United States and Europe, keeping the CVP low during liver transplantation seems to be critical for anesthesia management. Although there is no clear evidence for its ideal level, the CVP is generally kept between 5 and 10 cm H$_2$O. However, it is important to note that lower CVP values could be a reason for hypotension and deterioration of microperfusion in grafts. A CVP significantly higher than 10 cm H$_2$O is a cause of liver congestion, deterioration of liver function, and substantial coagulopathy. This is one of the reasons for relatively restrictive volume management, using blood products (FFP or PRBCs units) and albumin to increase colloid osmotic pressure, with only limited infusion of normal saline.

New modalities for volume and cardiac status monitoring include increasing the use of TEE intraoperatively instead of a SG catheter. The role of non-invasive cardiac output devices (e.g., esophageal Doppler, arterial line pulse contour analysis, etc.) is continually increasing.

**Correction of Coagulation**

Keeping the CVP in the desired range is very difficult in cases where there is both coagulopathy and a need to administer blood products. In the United States, the blood products available for correction of intra- or postoperative coagulopathy include FFP, platelets, and cryoprecipitate. In Europe there are some additional
treatment possibilities that are not currently available in the United States due to a lack of FDA approval. Prothrombin complex concentrate (PCC; also called PPSB in Germany and Beriplex P/N in the UK) can significantly improve coagulation with only minimal volume expansion. It was first successfully applied in 1959. Since then, this agent has frequently been used in situations of extensive coagulopathy. The medication consists of a combination of balanced coagulation factors (Factor II Prothrombin, Factor VII Proconvertin, Factor X Stuart-Prower-Factor, Factor IX antihemophilic Factor, Protein C, Protein S, Protein Z, AT III [15-30 U], and Heparin [250 U]). Depending on the situation, a dose of 1200 U-3000 U is necessary for significant improvement of coagulation. Every 600 U must be dissolved in 20 ml fluid. This means that volume exposure is 40-100 ml for the optimization of coagulation. The alternative to PCC is giving FFP units with extensive amounts of volume (each unit is about 250 ml). The use of PCC is very favorable, especially in situations where there is already a high CVP level. PCC can significantly improve coagulation in a very short period of time, which is desirable in many clinical situations.

This is a major reason why PCC is used in Europe as widely as it is; not only for liver transplantation, but also for a variety of specific clinical situations in which coagulation is compromised and it is necessary to quickly prepare a patient for surgery. Use of the medication is safe when applied according to recommendations. The possibility of thrombosis is a major complication of this medication. The first report about DIC after using PCC was published in 1959. Other possible thrombotic complications are: deep vein thrombosis, myocardial infarction, and lung embolism. Allergic reactions were described after application of PCC as well. An additional problem with this medication is its extremely high cost: for this reason, only a senior hematologist may prescribe this medication in the UK.

A further difference between Europe and the United States is the availability of fibrinogen for transfusions in the former but not in the latter. The medication is not FDA approved in the United States, and thus the transfusion of cryoprecipitate is the only possibility to adjust fibrinogen levels. Cryoprecipitate is available in Europe as well, but an infusion of fibrinogen is preferred because it allows administration of the medication in a more precise, faster manner, and with less volume exposure. Fibrinogen is available in powder form, and the volume amount that is necessary for infusion is comparable with PCC. The adverse effects after administering fibrinogen are similar to those after administering PCC: thrombosis and allergic reactions. With careful use, and taking into account all advantages and disadvantages, the administration of fibrinogen is safe and has been widely used in European countries for correction of impaired coagulation.

Aprotinin has been used for many years in liver transplantation. There are many publications that demonstrate blood product transfusions can be reduced with a prophylactic infusion of a low dose of aprotinin. Generally, the prophylactic use of antifyibrinolytics is very controversial. Nowadays, its use in veno-venous bypass for liver transplantation is very rare, and we no longer expect the activation of plasmin and fibrinolytic cascade. Discussion about the prophylactic use of this group of medications has existed for several years, and we currently have no clear answer. Aprotinin was withdrawn from the market in 2008 in the United States and Europe and can be used only for studies on cardiopulmonary bypasses. Different centers in the United States and Europe have started the use of tranexamic acid and epsilon aminocaproic acid, which have a mechanism of action similar to aprotinin. Although the publications show a slightly higher evidence of arterial and venous thrombosis in patients with tranexamic acid and epsilon aminocaproic acid treatment in comparison to those where aprotinin was applied, its impact on clinical practice is not completely clear.

The use of thromboelastography (TEG) for coagulation management, both in the United States and in Europe, constitutes the more recent trend in coagulation monitoring. The method is relatively old and was first...
described by the German researcher Helmut Hartert in 1948. In contrast to traditional coagulation studies, TEG is a relatively simple procedure to analyze clot formations under dynamic conditions. TEG measures the viscoelastic properties of blood as it is induced to clot under a low shear environment resembling sluggish venous flow. The patterns of changes in shear elasticity enable the determination of the kinetics of clot formation and growth as well as the strength and stability of the formed clot. This procedure allows the exact determination of coagulopathy. TEG has not been implemented in clinical practice for many years. In 1980, anesthesiologists in the United States began using the procedure routinely for liver transplantations. In Europe, the application of thromboelastogram is not the standard of care. In Germany, TEG has been on the market since about 2000, and many transplantation centers have begun its use in special clinical situations. A large number of publications have shown that thromboelastography can recognize coagulation problems faster, more specifically, and sometimes in situations when the coagulation profile is still normal. TEG was a significantly better predictor (87% accuracy) of postoperative hemorrhages and the need for reoperation than the activated clotting time ACT (30% accuracy) or coagulation profile (51% accuracy). Our expectation is that TEG will be the routine standard of care in the near future for liver transplantation.

Postoperative Care for Liver Transplantation Patients

The organization of postoperative care for liver transplantation patients in the United States is somewhat different than in Europe. In the United States, surgeons are the usual care providers, and anesthesiologists (and other specialists) are involved in the postoperative care for transplant patients only occasionally, in particular in the big centers. In Europe the main emphasis in the education of anesthesiologists is placed on critical care; consequently, the majority of SICUs are run by anesthesiologists. Teams on the transplantation SICU usually consist of up to 50% of anesthesiologists and 50% of surgeons, and we believe that this cooperation might significantly improve the quality of care. The next significant difference between the United States and Europe is the absence of separate care for different services (i.e., in Europe the same team is usually responsible for maintenance of postoperative care, nutrition, ventilation, antibiotic therapy and immunosuppression). This approach requires additional training for the SICU team members but enables them to provide care more consistently and improves the flow of information.

In the United States discharge from the intensive care unit occurs much faster in uncomplicated cases (less than 24 hours) than in Europe, where the ICU stay is five days and more.

Early extubation became the gold standard in Europe in order to prevent postoperative pulmonary infections in patients with a high level of immunosuppression, as well as to improve hemodynamic stability and to facilitate easier neurologic monitoring of patients. Certainly, early extubation requires closer observation and monitoring of patients especially on the first and second day after the operation, but involvement of anesthesiologists in ICUs with expertise in the area of airway management makes the process easier. In the United States the extubation of transplant patients in the operating room at the end of surgery is becoming more and more popular but, unfortunately, does not have widespread acceptance, especially among surgeons.

It is important, however, to note that even if centers in the United States have a shorter length of stay than centers in other countries, this does not translate into overall lower costs.

Conclusion
Liver transplantation has become a remarkably successful project, offering critically ill people a new chance to achieve a good quality of life. With the improvement of surgery and anesthesia techniques and the use of newer medications for immunosuppression, patient and graft survival have been vastly improved. Currently, the longest patient survival rate is more than thirty years after a successful liver transplantation. Liver transplantation is an example of how an extremely complex procedure requires close cooperation between different specialties.

The United States and Western Europe have some of the biggest transplantation centers in the world. The development of transplantation programs on both continents took slightly different paths, but with very similar final results. Many countries that were not very active in this area now recognize the ethical and financial advantage of liver transplantation and have started, or are about to start, their own programs with the aim of achieving established standards.

Despite different program lengths and experiences, the anesthesia management for liver transplantation is becoming increasingly convergent. The difference in the structure of the transplantation service, the transplantation procedure and postoperative care do not have a major influence on the final outcome. Few differences in anesthesia management, none of them in critical areas, have been observed. In Europe, the wider choice of medications, especially for coagulation adjustment, allows the transplant anesthesiologist more flexibility in the management of transplantation patients but it does not improve results significantly.

In the United States, the cost of liver transplantation is higher despite a significantly shorter postoperative hospital stay. At the same time, the outcomes in the United States are similar to Europe, with a patient survival rate of 88% at one year and 72% at five years. In the current financial situation, both continents are claiming a reduction in costs, but it is very likely that expenses in the United States will be higher in comparison to Europe due to the structure of the health care system and the significantly higher price of medications. It is expected that the process of unification in the management of liver transplantations will further progress, and with recent pressure on reducing health care costs, the difference between the United States and Europe will gradually diminish even further.
Intraoperative blood salvage during liver transplantation.

D. S. L. transplantation_1 http://www.ispub.com/journal/the_internet_journal_of_pharmacology/volume_2_number_1_50/article/the_history_of_liver_and_renal

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P. of the liver, biliary tract, and pancreas

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K. Intraoperative blood salvage during liver transplantation.

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INDUCED HYPOCAPNIA IS EFFECTIVE IN TREATING PULMONARY HYPERTENSION FOLLOWING MITRAL VALVE REPLACEMENT

MIRZA MAHDI, MD, NINOS J. JOSEPH, BS, DIVINA P. HERNANDEZ, RN, BSN, GEORGE J. CRYSTAL, PhD, FAHA, ANIS BARAKA, MD, FRCA AND M. RAMEZ SALEM, MD

Abstract

Background: Mitral valve stenosis is often associated with increased pulmonary vascular resistance resulting in pulmonary hypertension, which may lead to or exacerbate right heart dysfunction. Hypocapnia is a known pulmonary vasodilator. The purpose of this study was to evaluate whether induced hypocapnia is an effective treatment for pulmonary hypertension following elective mitral valve replacement in adults.

Methods: In a prospective, crossover controlled trial, 8 adult patients with mitral stenosis were studied in the intensive care unit following elective mitral valve replacement. Hypocapnia was induced by removal of previously added dead space. Normocapnic (baseline), hypocapnic and recovery hemodynamic parameters including cardiac output, pulmonary vascular resistance, pulmonary artery pressure and systemic oxygen delivery and consumption were recorded.

Results: Moderate hypocapnia (an end-tidal carbon dioxide concentration reduced to 28 ± 5 mmHg) resulted in decreases in pulmonary vascular resistance and mean pulmonary artery pressure of 33% and 25%, respectively. Hypocapnia had no other hemodynamic or respiratory effects. The changes in pulmonary vascular resistance and mean pulmonary artery pressure were reversible.

Conclusion: Moderate hypocapnia was effective in decreasing pulmonary vascular tone in adults following mitral valve replacement. The application of this maneuver in the immediate postoperative period may provide a bridge until pulmonary vascular tone begins to normalize following surgery.

Introduction

Mitrval stenosis is one of the most common diseases of the atrio-ventricular valves. Although rheumatic fever, the most frequent cause of mitral stenosis, has been largely eliminated in the West, it remains a major health problem in Third World countries. Less frequent causes of mitral valve stenosis are congenital heart disease, systemic lupus erythematosus, atrial myxoma, malignant carcinoid, and bacterial endocarditis. Treatment of symptomatic mitral stenosis often involves mitral valve repair or replacement.

Mitrval valve stenosis is often associated with pulmonary hypertension. Traditionally, pulmonary...
hypertension has been treated with intravenous vasodilators, including sodium nitroprusside\textsuperscript{2}, nitroglycerin\textsuperscript{3,4}, prostaglandin E\textsubscript{1}\textsuperscript{5}, isoproterenol\textsuperscript{6}, amrinone and milrinone\textsuperscript{7}, and diazoxide\textsuperscript{8}. However, the use of these drugs is limited by a lack of pulmonary vascular selectivity, and, in some cases, by a prolonged elimination half-life\textsuperscript{4,9}. More recently, nitric oxide gas and other inhaled vasodilators\textsuperscript{2,3,10-19} have been popularized because their use results in selective pulmonary effects and limited systemic effects. However, the use of nitric oxide gas is expensive, requires a special delivery system, and results in rebound pulmonary hypertension following discontinuation\textsuperscript{19}. A recent study has demonstrated that inhalation of milrinone, a drug that may be free of these aforementioned shortcomings, attenuated pulmonary hypertension in a rat model of congestive heart failure\textsuperscript{20}. Although these findings are promising, their applicability to the patient with pulmonary hypertension following mitral valve repair remains to be determined.

It is well established that the partial pressure of carbon dioxide (PaCO\textsubscript{2}) is an important physiologic determinant of pulmonary vascular tone\textsuperscript{21}. Previous findings in laboratory animals\textsuperscript{22,23} and humans\textsuperscript{12,24-26} have shown that hypocapnia can cause significant pulmonary vasodilating actions. Furthermore, Drummond and colleagues\textsuperscript{27} demonstrated that reducing PaCO\textsubscript{2} produced a consistent and reproducible reduction in pulmonary vascular resistance in infants with pulmonary hypertension. Whether this intervention is also effective in adults is unknown and requires investigation. The current study tested the hypothesis that moderate hypocapnia can be an effective maneuver for decreasing pulmonary vascular resistance in adult patients undergoing mitral valve surgery.

**Methods**

After approval by the Illinois Masonic Medical Center Institutional Review Board, written and signed informed consent was obtained from 21 patients with severe mitral valve stenosis, as defined by a mitral valve area smaller than 1 cm\textsuperscript{2} based on echocardiography and cardiac catheterization, scheduled for elective mitral valve replacement at Illinois Masonic Medical Center. Inclusion criteria were age over 18 years, and a preoperative pulmonary vascular resistance greater than 200 dyn\textperiodcentered s\textperiodcentered cm\textsuperscript{5} (normal range 50 to 150 dyn\textperiodcentered s\textperiodcentered cm\textsuperscript{5}). Exclusion criteria were a history of lung disease (evidence of chronic obstructive lung disease or end-stage emphysema), diagnosis of both mitral valve stenosis and severe mitral regurgitation, multiple valve replacements, combined mitral valve and coronary artery bypass procedures, mitral valve repair, and a preoperative requirement for intravenous vasodilators or inotropic drugs or a ventricular assist device. We cannot preclude the possibility that some patients that were allowed to participate in the study had a mild degree of mitral regurgitation.

Upon arrival to the operating room, standard monitors, including 5-lead electrocardiogram, noninvasive arterial blood pressure, and pulse oximetry, were applied. A catheter was placed in a radial artery for continuous measurement of arterial blood pressure and blood sampling. A 7F or 7.5F balloon-tipped thermodilution catheter was placed in the right internal jugular vein and positioned in the pulmonary artery for monitoring of pulmonary artery and pulmonary capillary wedge pressures, measurement of cardiac output, and sampling mixed venous blood. Preoperative hemodynamic data and arterial and mixed venous blood gases were obtained immediately prior to induction of anesthesia. Anesthesia was induced and maintained with fentanyl (100 mcg/kg) supplemented with isoflurane (1\%-2\% in oxygen). Cardiopulmonary bypass was instituted using crystalloid priming. Muscle relaxation was induced and maintained with vecuronium. Core temperature was continuously monitored via a nasopharyngeal probe. Inspired and end-tidal carbon dioxide
were continuously monitored. The effects of all anesthetic drugs were allowed to reverse spontaneously.

After the completion of mitral valve replacement, an additional dose of vecuronium (0.5 mg/kg) was administered and the patient was transferred to the surgical intensive care unit. Postoperative mechanical ventilation was maintained with the use of synchronized intermittent mandatory ventilation mode with a tidal volume of 10 mL/kg, a rate of 10 breaths/min, an inspired oxygen fraction of 0.6 to 1.0, and a positive end-expiratory pressure of 5 cm H₂O. The ventilator (Bennett MA1, Puritan Bennett, USA) was initially adjusted to obtain a value for PaCO₂ between 37 and 44 mmHg.

The prospective, crossover, controlled study protocol commenced after the following criteria were met: 1) at least two hours had elapsed since arrival of the patient in the surgical intensive care unit, 2) the patient had exhibited no spontaneous ventilatory efforts, and 3) two hours had elapsed following discontinuation of any cardioactive drug. The inspired oxygen fraction was then increased to 1.0. A technique of “constant volume hyperventilation”, was employed to induce hypocapnia with minimal changes in lung mechanics. This was accomplished by initially increasing tidal volume by 200 mL while adding 200 mL mechanical dead space distal to the Y-piece, thus yielding a baseline normocapnic condition. A 30-min equilibration period was allowed, after which hemodynamic measurements and blood gases/pH were obtained. Moderate hypocapnia, defined as a PaCO₂ between 30 and 35 mmHg, was then instituted by removal of the dead space without changing the ventilator settings. End-tidal carbon dioxide concentration was continuously monitored and used as an index of alveolar carbon dioxide concentration. After 30 minutes of hypocapnia, blood gases/pH and the hemodynamic measurements were repeated. Thereafter, the dead space tubing was returned to the breathing circuit in order to restore normocapnia. Thirty minutes later, a set of recovery values of measured and calculated hemodynamic and respiratory parameters was obtained (Table 1). Following conclusion of the study protocol, the dead space tubing was removed and the tidal volume and inspired oxygen fraction were returned to the pre-experimental settings, i.e., tidal volume of 10 to 15 mL/kg, rate of 10 breaths/min, inspired oxygen fraction of 0.6 to 1.0, and positive end-expiratory pressure of 5 cm H₂O.

Table 1: Measured and calculated parameters recorded at each measurement period

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Measured or Calculated</th>
<th>Equation for Calculated Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate (beats/min)</td>
<td>Measured</td>
<td></td>
</tr>
<tr>
<td>Mean Arterial Blood Pressure (mmHg)</td>
<td>Measured</td>
<td></td>
</tr>
<tr>
<td>Stroke Volume (cc)</td>
<td>Calculated</td>
<td>CO/HR</td>
</tr>
<tr>
<td>Cardiac Output (L/min)</td>
<td>Measured</td>
<td></td>
</tr>
<tr>
<td>Cardiac Index (L·min⁻¹·m⁻²)</td>
<td>Calculated</td>
<td>CO/BSA</td>
</tr>
<tr>
<td>Mean Central Venous Pressure (cm H₂O)</td>
<td>Measured</td>
<td></td>
</tr>
<tr>
<td>Mean Pulmonary Artery Pressure (mmHg)</td>
<td>Measured</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Capillary Wedge Pressure (mmHg)</td>
<td>Measured</td>
<td></td>
</tr>
</tbody>
</table>
### Table

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Calculation Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway Pressure (cm H₂O)</td>
<td>Measured</td>
</tr>
<tr>
<td>Pulmonary Vascular Resistance (dyn·s·cm⁻²)</td>
<td>Calculated 80 x (MPAP - PCWP)/CO</td>
</tr>
<tr>
<td>Systemic Vascular Resistance (dyn·s·cm⁻²)</td>
<td>Calculated 80 x (MAP - CVP)/CO</td>
</tr>
<tr>
<td>Arterial Blood Gases/pH</td>
<td>Measured</td>
</tr>
<tr>
<td>Hemoglobin (gm/dL)</td>
<td>Measured</td>
</tr>
<tr>
<td>Mixed Venous Blood Gases/pH</td>
<td>Measured</td>
</tr>
<tr>
<td>End-tidal carbon dioxide tension (mmHg)</td>
<td>Measured</td>
</tr>
<tr>
<td>Skin &amp; blood temperature (°C)</td>
<td>Measured</td>
</tr>
<tr>
<td>Inspired oxygen fraction</td>
<td>Measured</td>
</tr>
<tr>
<td>Arterial Oxygen Saturation (%)</td>
<td>Measured</td>
</tr>
<tr>
<td>Mixed Venous Oxygen Saturation (%)</td>
<td>Measured</td>
</tr>
<tr>
<td>Whole Body Oxygen Consumption (mL O₂/min)</td>
<td>Calculated CO/(150 - [PaCO₂ x 1.25] - PaO₂)</td>
</tr>
<tr>
<td>Oxygen Delivery (mL O₂/100 mL)</td>
<td>Calculated 10 x [Hgb x 1.36 x SaO₂] + [0.0031 x PaO₂]/CO</td>
</tr>
</tbody>
</table>

### Statistical Analysis

Statistical analysis was performed using SPSS version 15.0 (SPSS, Chicago, IL). A repeated measures one-way analysis of variance and the least significance difference tests were employed to detect significant differences in continuous variables between the time periods. Statistical significance was accepted when $p < 0.05$. All values are presented as mean ± standard deviation (SD).

### Results

Following induction of anesthesia but prior to the institution of cardiopulmonary bypass, eleven patients with pulmonary vascular resistance greater than 200 dyn·s·cm⁻² were considered eligible for continued participation in the study (Fig. 1 and Table 2). Noteworthy are the values for pulmonary vascular resistance and mean pulmonary artery pressure of 300 ± 78 dyn·s·cm⁻² and 27 ± 7 mmHg, respectively. The number of eligible subjects was further reduced following surgery when 2 patients required prolonged intravenous infusion of vasopressors or vasodilators and one patient exhibited inspiratory efforts in the postoperative period. Data analysis was performed on the remaining eight patients (3 males and 5 females), who satisfied the study criteria (Fig. 1).
Flow diagram illustrating subject recruitment and disqualification because of application of exclusion criteria. The study protocol was completed in 8 of the 21 subjects who were originally enrolled.

21 patients screened and consented

11 patients with preoperative PVR > 200 dyn•s•cm⁻⁵

- 2 patients receiving iv vasopressors or vasodilators
- 1 patient exhibited inspiratory efforts

8 patients with postoperative PVR > 200 dyn•s•cm⁻⁵
Table 2

Measured and calculated parameters recorded prior to institution of cardiopulmonary bypass

<table>
<thead>
<tr>
<th>Measured/Calculated Parameter</th>
<th>Mean ± Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Output (L/min)</td>
<td>4.0 ± 1.0</td>
</tr>
<tr>
<td>Cardiac Index (L•min⁻¹•m⁻²)</td>
<td>2.3 ± 0.6</td>
</tr>
<tr>
<td>Heart Rate (beats/min)</td>
<td>78 ± 13</td>
</tr>
<tr>
<td>Mean Arterial Pressure (mmHg)</td>
<td>86 ± 8</td>
</tr>
<tr>
<td>Central Venous Pressure (cm H₂O)</td>
<td>12 ± 2</td>
</tr>
<tr>
<td>Mean Pulmonary Artery Pressure (mmHg)</td>
<td>27 ± 7</td>
</tr>
<tr>
<td>Pulmonary Capillary Wedge Pressure (mmHg)</td>
<td>14 ± 5</td>
</tr>
<tr>
<td>Stroke Volume (mL)</td>
<td>52 ± 14</td>
</tr>
<tr>
<td>Pulmonary Vascular Resistance (dyn•s•cm⁻⁵)</td>
<td>300 ± 78</td>
</tr>
<tr>
<td>Systemic Vascular Resistance (dyn•s•cm⁻⁵)</td>
<td>1446 ± 398</td>
</tr>
<tr>
<td>Intrapulmonary Shunt (%)</td>
<td>11.3 ± .8</td>
</tr>
<tr>
<td>Alveolar-to-Arterial Oxygen Difference (mmHg)</td>
<td>231.0 ± 90.9</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.41 ± .06</td>
</tr>
<tr>
<td>Arterial Carbon Dioxide Tension (mmHg)</td>
<td>39 ± 3</td>
</tr>
<tr>
<td>Arterial Oxygen Tension (mmHg)</td>
<td>375 ± 121</td>
</tr>
<tr>
<td>Tidal Volume (cc)</td>
<td>813 ± 63</td>
</tr>
<tr>
<td>Peak Airway Pressure (cm H₂O)</td>
<td>31 ± 1</td>
</tr>
<tr>
<td>End-tidal Carbon Dioxide Tension (mmHg)</td>
<td>40 ± 3</td>
</tr>
<tr>
<td>Respiratory Rate (breaths/min)</td>
<td>10 ± 1</td>
</tr>
<tr>
<td>Hemoglobin (gm/dL)</td>
<td>12.8 ± 1.1</td>
</tr>
</tbody>
</table>

Data are mean ± the standard deviation.

Tables 3 and 4 present the effects of induced hypocapnia on pulmonary vascular resistance, mean pulmonary artery pressure, and associated parameters. A reduction in end-tidal carbon dioxide from 39 ± 8 to 28 ± 5 mmHg and the attendant reduction in PaCO₂ from 42 ± 6 to 33 ± 4 mmHg and increases in both arterial and venous pH from 7.38 ± 0.07 and 7.33 ± 0.6 to 7.47 ± 0.06 and 7.40 ± 0.6, respectively, were associated with decreases in mean pulmonary vascular resistance and mean pulmonary artery pressure of 33% and 25%, respectively (Tables 3 and 4 and Figure 2). Other hemodynamic and oxygen supply/demand parameters were not affected. The decreases in pulmonary vascular resistance and mean pulmonary artery pressure associated with hypocapnia returned to the normocapnic values during recovery (Tables 3 and 4 and Fig. 2).

Table 3

Measured or calculated hemodynamic parameters recorded at normocapnia, induced hypocapnia, and after recovery (normocapnia)

<table>
<thead>
<tr>
<th>Measured/Calculated Parameter</th>
<th>Normocapnia</th>
<th>Hypocapnia</th>
<th>Recovery (normocapnia)</th>
<th>p-value</th>
</tr>
</thead>
</table>

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Cardiac Output (L/min) & 4.5 ± 0.8 & 4.4 ± 1.0 & 4.6 ± 0.9 & 0.692 \\
Cardiac Index (L•min⁻¹•m⁻²) & 2.7 ± 0.5 & 2.7 ± 0.6 & 2.7 ± 0.5 & 0.577 \\
Mean Pulmonary Artery Pressure (mmHg) & 28 ± 6 & 21 ± 6* & 29 ± 5 & 0.049 \\
Pulmonary Vascular Resistance (dyn•s•cm⁻⁵) & 246 ± 117 & 165 ± 80* & 256 ± 122 & 0.044 \\
Heart Rate (beats/min) & 77 ± 15 & 77 ± 14 & 74 ± 13 & 0.943 \\
Mean Arterial Pressure (mmHg) & 85 ± 12 & 81 ± 9 & 80 ± 10 & 0.551 \\
Central Venous Pressure (cm H₂O) & 11 ± 3 & 12 ± 4 & 11 ± 3 & 0.890 \\
Pulmonary Capillary Wedge Pressure (mmHg) & 15 ± 4 & 16 ± 5 & 15 ± 5 & 0.691 \\
Systemic Vascular Resistance (dyn•s•cm⁻⁵) & 1347 ± 305 & 1283 ± 283 & 1237 ± 234 & 0.601 \\

* Statistical significance from any other period (p < 0.05)
Data are mean ± the standard deviation.

Table 4
Measured or calculated respiratory parameters recorded at normocapnia, induced hypocapnia, and after recovery (normocapnia).

<table>
<thead>
<tr>
<th>Measured/Calculated Parameter</th>
<th>Normocapnia</th>
<th>Hypocapnia</th>
<th>Recovery (normocapnia)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-tidal Carbon Dioxide Tension (mmHg)</td>
<td>39 ± 8</td>
<td>28 ± 5*</td>
<td>39 ± 8</td>
<td>0.011</td>
</tr>
<tr>
<td>Airway Pressure (cm H₂O)</td>
<td>35.7 ± 6.6</td>
<td>36.7 ± 6.9</td>
<td>35.1 ± 4.7</td>
<td>0.511</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.38 ± 0.07</td>
<td>7.47 ± 0.06*</td>
<td>7.38 ± 0.07</td>
<td>0.013</td>
</tr>
<tr>
<td>Arterial Carbon Dioxide Tension (mmHg)</td>
<td>42 ± 6</td>
<td>33 ± 4*</td>
<td>43 ± 6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arterial Oxygen Tension (mmHg)</td>
<td>328 ± 109</td>
<td>307 ± 101</td>
<td>342 ± 101</td>
<td>0.716</td>
</tr>
<tr>
<td>Mixed Venous pH</td>
<td>7.32 ± 0.06</td>
<td>7.40 ± 0.06*</td>
<td>7.32 ± 0.07</td>
<td>0.047</td>
</tr>
<tr>
<td>Mixed Venous Carbon Dioxide Tension (mmHg)</td>
<td>50.9 ± 5.3</td>
<td>41.4 ± 2.5*</td>
<td>49.03 ± 4.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Mixed Venous Oxygen Tension (mmHg)</td>
<td>46.3 ± 11.7</td>
<td>39.5 ± 9.4</td>
<td>45.6 ± 11.1</td>
<td>0.443</td>
</tr>
<tr>
<td>Systemic Oxygen Consumption (mL•min⁻¹•m⁻²)</td>
<td>5983 ± 116.7</td>
<td>592 ± 134.9</td>
<td>606.0 ± 116.6</td>
<td>0.969</td>
</tr>
<tr>
<td>Whole body Oxygen Delivery (mL•min⁻¹•m⁻²)</td>
<td>220.6 ± 171.9</td>
<td>246.2 ± 154.3</td>
<td>234.9 ± 155.7</td>
<td>0.938</td>
</tr>
</tbody>
</table>

* Statistical significance from any other period (p < 0.05)
Data are mean ± the standard deviation.
Fig. 2
Pulmonary vascular resistance (PVR) and end-tidal carbon dioxide concentration (PETCO$_2$) obtained during normocapnia, induced hypocapnia and following return to normocapnia (recovery). Data presented as mean ± standard deviation.

* denotes statistically significant difference from all other time periods ($p < 0.05$).

There were no adverse events or complications associated with the conduct of this study. All patients’ tracheas were extubated within two to six hours after completion of the study protocol.

Discussion

Increased pulmonary vascular resistance leading to pulmonary hypertension and right ventricular failure is frequently observed in patients with mitral valve stenosis. These conditions can often persist immediately following mitral valve surgery and can complicate management in the postoperative period$^{30}$. Pathophysiologic mechanisms contributing to increased pulmonary vascular resistance and pulmonary hypertension include: 1) an increased left atrial pressure transmitted retrogradely into the pulmonary arterial circulation, 2) vascular remodeling of the pulmonary vasculature in response to chronic obstruction of pulmonary venous drainage, and 3) pulmonary vasoconstriction$^{30,31}$. Although mitral valve replacement has been frequently demonstrated to eliminate the increased left atrial pressure$^{31}$, the other contributing factors persist following mitral valve surgery. Vascular remodeling is a “fixed” component$^3$ and is not responsive to perioperative interventions. On the other hand, pulmonary vasoconstriction is a “reactive” component that can be manipulated in the
INDUCED HYPOCAPNIA IS EFFECTIVE IN TREATING PULMONARY HYPERTENSION FOLLOWING MITRAL VALVE REPLACEMENT

It is well established that hypocapnia can cause changes in the distribution of cardiac output and regional blood flow. In the systemic circulation, the change in blood flow is the result of the balance between the vasodilating effect of an attenuated sympathetic vasoconstrictor nerve discharge secondary to reduced activation of the arterial chemoreceptors, e.g., the carotid bodies, and the local ability of hypocapnic alkalosis to directly cause an increase in vascular smooth muscle tone, i.e., vasoconstriction. Unlike the systemic circulation, hypocapnia has a vasodilating effect in the pulmonary circulation. This unique behavior is attributable to the ability of hypocapnic alkalosis to cause an increase in production of prostacyclin, a powerful vasodilator in the pulmonary endothelial cells, while having no effect on prostacyclin levels in systemic endothelial cells. Another fundamental difference between the pulmonary circulation and the systemic circulation relates to the local hypocapnic stimulus controlling vascular tone. Because the alveolar capillaries constitute an air-blood exchange interface, a reduction in alveolar PCO₂ (PAO₂) is the primary stimulus for pulmonary vasodilation, although a reduction in mixed venous PCO₂ (PvO₂) may also play a role.

As reviewed by Laffey and Kavanagh, hypocapnia can have an impact on the balance between cerebral oxygen supply and demand. This is a major concern when hypocapnia is induced deliberately, is accidental or disease related. Hypocapnia can reduce oxygen supply by causing cerebral vasoconstriction and a leftward shift in the oxyhemoglobin dissociation curve (which can impair unloading of oxygen at the tissue level).

A mild form of hypocapnia (PETCO₂ of 28 ± 5 mmHg) was induced in the present study to minimize its effects in the brain. The findings demonstrated that hypocapnia of this degree was capable of producing pronounced decreases in mean pulmonary artery pressure and pulmonary vascular resistance. In the absence of cerebral oximetry we had no direct measurement of its effect on cerebral oxygenation. However, previous studies have shown that the decrease in PCO₂ that we evaluated causes an approximate 20% reduction in cerebral blood flow. It is well established that the brain has a considerable oxygen extraction reserve which should be capable of offsetting this decrease in cerebral blood flow, despite an impairment to oxygen unloading. Moreover, previous work in our laboratory has demonstrated the cerebral vasconstrictor effect of hypocapnia is obtunded during hemodilution, which would have an ameliorating influence on the hypocapnia-induced decreases in cerebral blood flow in the subjects of this study.

The advantages of induced hypocapnia were that it was easily applied in the mechanically ventilated patient, required no added expense, had an immediate effect, and showed no degradation. In addition, induced hypocapnia was easily reversed, was not associated with any significant systemic hemodynamic effects, and showed no rebound effects in the pulmonary circulation.

Several limitations of the study warrant address. First, the present study only evaluated the effect of hypocapnia in patients with pulmonary hypertension from mitral valve stenosis. Thus, extrapolation of the findings to patients with pulmonary hypertension from other causes would be inappropriate. Second, a standard 30 min of duration of hypocapnia was evaluated. It is not known whether the reduction in pulmonary vascular resistance would persist for longer periods of hypocapnia. Third, a single moderate level of hypocapnia was examined. It remains to be determined whether the decrease in pulmonary vascular resistance is a threshold response or whether it will vary as a function of the degree of hypocapnia. Finally, the study would have benefited from transesophageal echocardiographic measurements to evaluate whether the hypocapnia-induced decreases in pulmonary artery pressure had a positive impact on the right ventricle, e.g., on right ventricular size, tricuspid regurgitation, or right ventricular strain.
In conclusion, the current findings provide preliminary evidence that moderate hypocapnia may be an effective and easily administered technique to reduce pulmonary vascular resistance in patients undergoing mitral valve surgery. In this role, the technique would provide a bridge until pulmonary vascular tone begins to normalize following surgery. Induced hypocapnia may have applications as an adjunct to other treatments for pulmonary hypertension.
References


Abstract

Introduction: Clevidipine is an ultra-short acting, intravenous calcium channel antagonist of the dihydropyridine class. Metabolism by blood and tissue esterases results in a half-life of 1-2 minutes thereby allowing easy titration by IV administration. We present preliminary experience with this novel agent to provide controlled hypotension (CH) in a cohort of adolescents undergoing posterior spinal fusion.

Methods: The records of patients ≤18 years of age who received clevidipine for CH were retrospectively reviewed. Demographic data included age, weight, gender, and co-morbid disease processes. Information regarding clevidipine included the initial infusion rate, time to achieve the target mean arterial pressure (MAP), the maintenance infusion rate, the average infusion rate, and the duration of administration. Hemodynamic information included the starting MAP and heart rate (HR) as well as the MAP and HR during the clevidipine infusion. Adverse effects related to clevidipine included excessive hypotension (need to discontinue the infusion or the need for a fluid bolus or administration of a vasopresor), tachycardia (20% increase in HR or the administration of a β-adrenergic antagonist) and elevated serum triglyceride level.

Results: The study cohort included 20 patients, ranging in age from 14 to 18 years and in weight from 46 to 96 kgs. To provide acceptable conditions for evoked potential monitoring, a total IV anesthetic technique was used. Propofol was started at 100 μg/kg/min and titrated to maintain the bispectral index at 40-60. Remifentanil was started at 0.1 μg/kg/min and increased up to 0.3 μg/kg/min as needed to control MAP. If the MAP was ≥65 mmHg, clevidipine was added to maintain the MAP at 50-65. The clevidipine infusion was started at 0.5-1 μg/kg/min and increased in increments of 0.5-1 μg/kg/min every 2-3 minutes to achieve the desired MAP. The target MAP was achieved within 5 minutes in 15 of the 20 patients and within 10 minutes in the other 5 patients. The maintenance infusion rate of clevidipine varied from 1-5 μg/kg/min (2.9 ± 0.7 μg/kg/min). With the administration of clevidipine, HR increased from a baseline of 76 ± 14 to 92 ± 11 beats/minute (p <0.05). The HR increase was ≥ 20 beats/minute in 4 patients. Intermittent doses of metoprolol were used in 3 patients to control the HR increase. No excessive hypotension was noted. A triglyceride level was drawn in 6 patients who received clevidipine with propofol and was elevated in 3 patients (≥150 mg/dL, high level 328 mg/dL). When the clevidipine infusion was discontinued, MAP returned to baseline within 5 minutes in 16 of the 20 patients and within 10 minutes in the other 4 patients.

Discussion: Clevidipine effectively controlled MAP and provided CH. Mild tachycardia was noted in
some patients with the occasional need for a β-adrenergic antagonist. No episodes of excessive hypotension were noted. Given its short half-life, clevidipine can be rapidly titrated to provide CH when changing levels of sympathetic stimulation may occur. Should inadvertent hypotension occur, its short duration of action offers an additional advantage over several other IV antihypertensive agents.

**Key words:** Clevidipine, calcium channel antagonist, controlled hypotension, spinal surgery

**Introduction**

Various techniques have been suggested as a means of limiting or avoiding the need for homologous blood transfusions. One such technique, controlled or deliberate hypotension (CH), involves the use of pharmacological agents to lower the mean arterial pressure (MAP) to 50-65 mmHg. Several different agents have been used to provide controlled hypotension including direct acting vasodilators (sodium nitroprusside, nitroglycerine), calcium channel antagonists (nicardipine), β-adrenergic antagonists, ganglion blocking agents, and the inhalational anesthetic agents.

Clevidipine (Cleviprex®, The Medicines Company, Parsippany, NJ 07054) is a short-acting, intravenous calcium channel antagonist of the dihydropyridine class. It undergoes rapid metabolism by non-specific blood and tissue esterases with a half-life of 1-3 minutes. It is currently approved by the Food & Drug administration for the reduction of blood pressure when oral therapy is not feasible or desirable. The majority of experience with this novel agent has been in the control of perioperative blood pressure in adults. There are only two reports regarding its use in pediatric-aged patients. We present our initial experience with clevidipine for CH during spinal surgery in adolescents.

**Methods**

These patients were cared for at the University of Missouri (Columbia, Missouri). This retrospective review and presentation of the data in this format were approved by the hospital’s Institutional Review Board. From the pharmacy database, patients who had received clevidipine for intraoperative CH during spinal surgery were identified. The following demographic data were obtained: age, weight, gender, and associated medical conditions. The intraoperative data included the anesthetic technique and agents used, duration of the surgical procedure, vertebral levels fused, estimated blood loss, fluids (including blood products) administered, and urine output. Information collected concerning clevidipine included the starting dose, time to achieve the desired MAP, mean infusion rate to maintain desired MAP, duration of the infusion, and the time to return of the MAP to baseline when the infusion was discontinued. The baseline heart rate and the maximum heart during the clevidipine infusion were recorded. Tachycardia was defined as a 20% increase in HR or the administration of a β-adrenergic antagonist. The intraoperative records were also reviewed for excessive hypotension defined as the need to turn off the infusion, the requirement for the administration of an adrenergic agonist (phenylephrine, ephedrine) or calcium, or the administration of a fluid bolus. When available, the triglyceride (TG) level obtained during the intraoperative infusion was noted. In the patients undergoing posterior spinal fusion, the baseline PaO₂ (prior to the start of clevidipine) and the lowest PaO₂ during the clevidipine infusion were recorded. Oxygenation data were collected only from patients undergoing posterior spinal fusion since it would have been difficult to determine whether alterations in oxygenation were related to the clevidipine infusion or the surgical procedure in patients undergoing thoracotomy, one-lung ventilation and
CLEVIDIPINE FOR CONTROLLED HYPOTENSION DURING SPINAL SURGERY IN ADOLESCENTS

anterior spinal fusion. Statistical analysis included a paired t-test to determine the statistical significance of any increase in heart rate or decrease in PaO₂ from baseline after the start of the clevidipine infusion. All data are presented as mean ± SD.

Results

DEMOGRAPHIC DATA: The study cohort included 20 patients, ranging in age from 14 to 18 years and in weight from 46 to 96 kgs. There were 11 boys and 9 girls. Underlying medical conditions included idiopathic scoliosis (n = 11), neuromuscular scoliosis from cerebral palsy (n = 8), and Duchenne’s muscular dystrophy (n = 1).

ANESTHETIC TECHNIQUE: The patient was held nil per os for 6 hours and transported to the operating room where routine American Society of Anesthesiologists’ monitors were placed. Anesthetic induction consisted of either inhalation induction with increasing concentrations of sevoflurane in nitrous oxide/oxygen or intravenous induction with propofol (3-4 mg/kg). Following anesthetic induction, endotracheal intubation was facilitated by a single dose of rocuronium (0.4-0.6 mg/kg). Core body temperature was monitored using an esophageal stethoscope. Depth of anesthesia was monitored using a bispectral index (BIS). A gauze pad that had been rolled was placed in the mouth to prevent lingual damage during neurophysiologic monitoring. Two large bore intravenous cannulae and an arterial cannula were placed in all patients. A central venous catheter was placed in 10 patients. To facilitate SSEP and MEP monitoring, total intravenous anesthesia (TIVA) was provided by continuous infusions of propofol, remifentanil and dexmedetomidine. No additional doses of a neuromuscular blocking agent were administered. The dexmedetomidine was started at 0.5 µg/kg/hour without a loading dose. The propofol was started at 100-120 µg/kg/min and titrated to maintain the BIS at 40-60. The remifentanil was started at 0.1 µg/kg/min and increased as needed to maintain controlled hypotension with a mean arterial pressure (MAP) of 50-65 mmHg. The patient was turned prone onto a Jackson table and a prone pillow to prevent pressure to the eyes and face. Once positioned prone, a forced air heating device was used to maintain normothermia. The antifibrinolytic agent, ε-amino caproic acid (EACA), was administered as a bolus dose of 100 mg/kg followed by an infusion of 10 mg/kg/hour until the wound was closed. Isotonic fluids were administered to provide maintenance fluids, correct the deficit, and replace third space losses and blood loss. All patients received 500 ml of a hydroxyethyl starch solution at the start of the procedure. As this was not a prospective study, the fluid therapy was not controlled. One peripheral IV or one port of the central line was used to administer lactated Ringer’s (50-100 mL/hour), remifentanil, propofol, dexmedetomidine, EACA, and clevidipine via infusion pumps. The other IV was used via a free flowing administration set and a fluid warmer to administer replacement fluids, colloids, and blood products as needed.

CLEVIDIPINE: If the MAP was ≥65 mmHg despite remifentanil at 0.3 µg/kg/min, clevidipine was added to maintain the MAP at 50-65. Clevidipine was administered using the standard commercially available solution (0.5 mg/mL). The clevidipine infusion was started at 0.5 µg/kg/min in 4 patients and at 1 µg/kg/min in 16 patients. The infusion was increased in increments of 0.5-1 µg/kg/min every 2-3 minutes to achieve the desired MAP. The target MAP was achieved at ≤5 minutes in 15 of the 20 patients and at ≤10 minutes in the other 5 patients. The mean time to achieve the desired MAP was 4.75 ± 2.2 minutes. The maintenance infusion rate of clevidipine varied from 1 to 5 µg/kg/min (2.9 ± 0.7 µg/kg/min). The clevidipine infusion was administered for 120 to 210 minutes (151.3 ± 27.9 minutes). With the administration of clevidipine, HR increased from a baseline of 76 ± 14 to 92 ± 11 beats/minute (p <0.05). The HR increase was ≥20 beats/minute in 4 patients.
Intermittent doses of metoprolol were used in 3 patients to control the HR increase. In the 14 patients undergoing posterior spinal fusion, the baseline PaO₂ decreased from 262 ± 19 mmHg to a low of 184 ± 16 mmHg during the clevidipine infusion (p < 0.1). When the clevidipine infusion was discontinued, the next PaO₂ value increased to 244 ± 21 mmHg (p = NS when compared to baseline). No excessive hypotension was noted. A triglyceride level was drawn in 6 patients who received clevidipine with propofol and was elevated in 3 patients (≥150 mg/dL, high level 328 mg/dL). When the clevidipine infusion was discontinued, MAP returned to baseline at ≤5 minutes in 16 of the 20 patients and at ≤10 minutes in the other 4 patients. The time for the MAP to return to baseline was 5.3 ± 2.4 minutes.

All patients maintained a urine output ≥ 2 mL/kg/hour during the period of controlled hypotension. The duration of the surgical procedures varied from 235 to 395 minutes (255 ± 38 min). The estimated blood loss varied from 2550 to 1800 mL (740 ± 288). Seven patients received homologous packed red blood cells. No other blood products were administered.

Discussion

Clevidipine shares similar structural and hemodynamic effects with nicardipine. Like nicardipine, it is an intravenous dihydropyridine calcium channel antagonist whose primary hemodynamic effect is vasodilatation of the arterial bed. Metabolism by non-specific blood and tissue esterases results in a half-life of 1-3 minutes. In adult cardiac surgical patients, Levy et al. prospectively compared clevidipine with placebo in adults who presented with preoperative hypertension defined as a systolic blood pressure (sBP) ≥140 mmHg. A clevidipine infusion ranging from 0.4 µg/kg/min to a maximum of 8 µg/kg/min reduced sBP by ≥15% in 92.5% of patients compared to only 17.3% of placebo patients. The median time to sBP control was 6 minutes (95% confidence interval: 6 to 8 minutes). A mild increase in HR was noted from 71 beats/minute to a maximum value of 84 beats/minute. There were no differences between clevidipine and placebo in regards to the adverse effect profile.

The ESCAPE-2 trial compared clevidipine (0.4 up to 8 µg/kg/min) with placebo in the treatment of postoperative hypertension (sBP ≥140 mmHg) in adult cardiac surgical patients. Systolic BP reduction ≥15% was achieved in 91.8% of the patients receiving clevidipine versus 20.4% with placebo (p < 0.0001). The median time to sBP control was 5.3 minutes (95% confidence interval: 4 to 7 minutes).

The potential utility of clevidipine has also been demonstrated in comparison to other antihypertensive agents. When comparing clevidipine with SNP, nitroglycerin or nicardipine for the treatment of acute hypertension in adult cardiac surgery patients, BP control was more effective with clevidipine than with nitroglycerin (p = 0.0006) or SNP (p = 0.003). No difference was noted when compared with nicardipine. Mortality was lower with clevidipine than sodium nitroprusside (p = 0.04).

To date, there are only two previous reports regarding the use of clevidipine in the pediatric-aged patient. The first study outlined the use of clevidipine pre-, intra- and postoperatively in doses ranging from 0.5 to 3.5 µg/kg/min in a cohort of 10 patients, ranging in age from 9 to 18 years. The clevidipine infusion was initiated at 0.5 µg/kg/min in 8 patients and at 1 µg/kg/min in the other 2 patients and then titrated up in increments of 0.5 µg/kg/min every 3-5 minutes to achieve effective BP control. The higher end of the dosing range was needed for the induction of controlled hypotension during spinal surgery. Two of the 10 patients required intermittent doses of metoprolol to control an associated increase in HR. No adverse effects such as
excessive hypotension were noted.

The second study reported effective postoperative BP control following cardiac surgery for congenital heart disease in 14 patients who ranged in age from 11 months to 15 years. Clevidipine was administered as either a continuous infusion or a bolus dose. The continuous infusion was used for control of either postoperative BP or intraoperative mean arterial pressure (MAP) during cooling and cardiopulmonary bypass (CPB) while the bolus dose was used for BP control during emergence from anesthesia. The continuous infusion was started at 1 μg/kg/min and increased in increments of 0.5-1 μg/kg/min. For postoperative BP control, dosing requirements varied from 1 to 7 μg/kg/min with the target BP achieved within 5 minutes in all patients. Two patients were treated with either intravenous or oral propranolol for an increase in HR. Effective control of MAP could not be achieved during CPB and cooling (core body temperature 28-32°C) even with doses as high as 10 μg/kg/min. Clevidipine was effective when administered as a bolus dose of 10-15 μg/kg to control BP during emergence from anesthesia.

For the first time, we report experience demonstrating the efficacy of clevidipine in providing CH during spinal surgery. The clevidipine infusion was started at either 0.5 or 1 μg/kg/min and increased in increments of 0.5-1 μg/kg/min every 2-3 minutes as needed. The desired MAP of 50–65 mmHg was achieved in less than 10 minutes in all of the patients at an average time of 4.75 minutes after starting the infusion. Maintenance infusion requirements varied from 1 to 5 μg/kg/min with an average of 2.9 μg/kg/min. When the clevidipine infusion was discontinued, MAP returned to baseline at ≤5 minutes in 16 of the 20 patients and at ≤10 minutes in the other 4 patients. The time for the MAP to return to baseline was 5.3 ± 2.4 minutes.

We found adverse effects to be relatively uncommon in our cohort of patients. No excessive hypotension was noted. However, as a vasodilator, it is not unexpected that reflex tachycardia may occur. This effect tended to be greater than that reported previously with nicardipine and also greater than that reported in adults trials with clevidipine. Although the effect was generally mild, treatment with a β-adrenergic antagonist was deemed necessary in 3 of the 20 patients and there was an average HR increase of 16 beats/minute in our cohort of patients. As a direct acting vasodilator, a second effect that was seen with clevidipine was a decrease in PaO₂ likely related to inhibition of hypoxic pulmonary vasoconstriction. This effect was not of clinical significance in our patient population, but should be considered in patients at risk for hypoxemia due to intrinsic lung disease. As clevidipine is administered in a lipid emulsion in a concentration of 0.5 mg/mL, a TG level was obtained in 6 patients who received clevidipine with propofol. The TG level was mildly elevated in 3 patients with a high value of 328 mg/dL (normal value: 50-150 mg/dL).

In summary, our initial clinical experience demonstrates the efficacy of clevidipine for CH during spinal surgery in adolescents. Given its rapid metabolism by tissue esterases, it can be easily titrated by continuous infusion to maintain the desired MAP with a rapid onset of action. Although its hemodynamic effects are similar to those of nicardipine, should adverse effects occur, its effect dissipate rapidly unlike those of nicardipine. Future studies, with a direct comparison to other commonly used agents, are needed to better define the role of clevidipine for CH and determine its advantages and disadvantages as well as its effects on estimated blood loss.
References

EFFECT OF PROPOFOL TITRATION V/S BOLUS DURING INDUCTION OF ANESTHESIA ON HEMODYNAMICS AND BISPECTRAL INDEX

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Abstract

Background: Propofol when given as 2 mg/kg I.V bolus for induction of anesthesia is known to cause hypotension requiring vasopressors. The objective of our study was to compare Propofol 2 mg/kg single IV bolus (Precalculated group, PG) with the titration of Propofol (Titration group, TG) to clinical parameters as 10 mg IV increments every 3 seconds on hemodynamic Parameters and Bispectral Index (BIS), during induction. The effect of titration on dose requirement for induction was also evaluated.

Methods: Effects on Hemodynamic parameters [Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP)], and vasopressors use were recorded at baseline and every 2 minute intervals for 10 minutes. The percent difference in HR, SBP, DBP, and MAP from baseline at 2, 4, 6, 8 and 10 minutes were calculated, to determine the effect on hemodynamic parameters. BIS was recorded at baseline, after injection of Propofol, at intubation and at 10 minutes. Dose requirement of Propofol in TG was also recorded.

Results: At 2 and 4 minutes, SBP decreased in PG by 21% and 18% vs. 11% and 9% in TG (p = .00 & .02); DBP decreased by 17% and 15% in PG vs. 5% and 4% in TG (p = .02 & .03); MAP decreased by 19% and 17% in PG vs. 5% and 4% in TG (p = .00 & .01). Vasopressors were required in 14/43 patients in PG vs. 5/41 in TG (p = .03). Titration resulted in 30% reduction in dose.

Conclusion: Titration of Propofol reduces hemodynamic changes, dose requirement and is able to achieve same level of BIS as in bolus.

Introduction

The properties like faster recovery and minimal postoperative complications has made propofol very popular intravenous anesthetic agent. It is the most commonly used intravenous agent for induction of general anaesthesia and is frequently administered in a dose of 2 mg/kg as a single I.V bolus. However, one of the

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known side effects of Propofol is to cause arterial hypotension with systolic blood pressure decreasing by as much as 30% or more\(^1\,\text{4}\). The mechanism of hypotension is attributed to a decrease in sympathetic activity\(^5\), myocardial depression\(^2\,\text{6,7}\), and direct vasodilation\(^1\,\text{2,6}\). Hypotensive effects of Propofol are generally proportional to the dose and rate of administration\(^2\,\text{3,8}\). Several studies have tried to address this by either reducing dose requirement\(^9\,\text{13}\) or changing the method of administration of propofol. Later studies involved slower infusion or titration of propofol and many of these studies employed Target controlled infusion system or infusion pumps. One such method is to incrementally increase the propofol dose till the loss of verbal response and eyelid reflex. It is very simple, used in day to day practice and does not require additional equipment. Despite, it is still a very common practice to administer propofol as a single IV bolus. We undertook this study to compare the two clinically adopted conventional methods of administering propofol; the standard method as 2 mg/kg single IV bolus with titration of propofol, given in 10 mg IV increments every 3 seconds, to clinical parameters. We evaluated the effect of these two methods on hemodynamic parameters, vasopressors use, and dose requirement of Propofol. In the later part of the study we also investigated the effect of these two methods on Bispectral index (BIS) to objectively assess the level of consciousness; and on hemodynamic changes occurring during intubation.

**Materials and Methods**

The study design is a prospective, single-blind, randomized-controlled trial. We learned through literature review of Propofol use during induction of anesthesia that all the studies had utilized 60-100 patients for comparison between 2 or 3 groups\(^1\,\text{4}\,\text{14}\,\text{17}\). They all had achieved statistical significance of < 0.05. Hence in our study we chose to compare the effect of Propofol administration as bolus or titration on hemodynamic parameters and BIS in 2 groups of 50 each for a total of 100 patients. After Institutional review board approval and written consent, 100 adult patients with a median age of 60 years (23-85 years) and ASA physical status 1-4 were studied.

They were scheduled for elective surgery under general anaesthesia requiring tracheal intubation. Patients who had a documented allergy to eggs and/or propofol were excluded from the study. Patient’s age, body weight, baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial blood pressure (MAP) were recorded before induction. Patients were allocated randomly by envelope method to group 1 (precalculated group, PG) or group 2 (titration group, TG). All patients were given Versed 2 mg, 2 minutes before propofol. They also received fentanyl, 100 µg for patients weighing 70 kg or more, and 50 µg for patients weighing less than 70 kg, and lidocaine 50 mg during induction. These drugs are given 1 minute before propofol. PG received propofol 2 mg/kg as a single IV bolus over 10 seconds. TG received propofol 10 mg every 3 seconds at the rate of 100 mg/30s until loss of verbal response and eyelid reflex. Subsequent neuromuscular blockade and tracheal intubation was achieved with succinylcholine or rocuronium as per anaesthesia providers and further anaesthesia was maintained with inhalational anesthetics. Hemodynamic parameters including HR, SBP, DBP and MAP were recorded every 2 minutes after induction until the 10 minute mark. Percentage difference in HR, SBP, DBP and MAP from the baseline at 2, 4, 8, 10 minutes were calculated. If vasopressors were required, ephedrine and/or Phenylephrine were used for hemodynamic stability. Criterion for using vasopressors was >20% decrease in SBP from baseline &/or decrease of SBP to <90 mmHg. The choice of drug was at the discretion of the anaesthesia provider.

Total propofol dose used and the number of patients requiring vasopressor was recorded until the 10
minute mark.

In titration method we required less amount of Propofol and there is a possibility that patient may not be asleep/unconscious. To answer that question we monitored our last 31 patients with BIS monitor to assess the level of consciousness. BIS was continuously monitored using BIS monitor (Aspect Medical System, Model A-2000, Natick, MA, USA) and the values were recorded at baseline, during induction, before & after intubation and at 10 minutes. In these patients we also aimed to investigate effect of PG and TG on hemodynamic changes occurring during intubation. The percentage difference in hemodynamic parameters (HR, SBP, DBP and MAP) from before intubation to immediately after intubation was compared between the two groups.

For Statistical analysis of hemodynamic parameters and propofol dose, Shapiro-Wilk test and Levene’s test was performed to determine normality assumption and to check for equality of variances. The samples with the normal distribution were analyzed by the independent sample T-test to determine the differences between groups. For Non-Normal Variables, Kruskal-Wallis Test was performed. Fisher exact test was used to compare the use of vasopressors in both groups. The software used is SPSS 17.0. P value <0.05 was considered significant.

Results

Patients with difficult tracheal intubations requiring multiple direct laryngoscopies, re-dosing of the propofol were not included for the analysis. Therefore, out of 100 patients enrolled in the study, 84 patients were analyzed (43 in PG; 41 in TG) for hemodynamic parameters, and 31 patients (16 in PG; 15 in TG) for BIS and for hemodynamic changes during intubation.

Demographic data (Table 1) were comparable for age, body weight and sex among both the groups. Baseline hemodynamic parameters-HR, SBP, DBP and MAP did not differ significantly among both the groups.

| Table 1 |
| Patient Characteristics (Age, Gender, ASA Status, Body Weight) and baseline hemodynamic parameters (Heart Rate, Systolic Blood Pressure, Diastolic Blood Pressure, Mean Arterial Pressure): Values are mean +/-SD or a number |

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Gender (M / F)</th>
<th>ASA Status 1/2/3/4</th>
<th>BW (kg)</th>
<th>HR (beat/min)</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>MAP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PG</td>
<td>58.1 ± 11.5</td>
<td>42 / 1</td>
<td>2/14/27/0</td>
<td>90.3 ± 16.4</td>
<td>68.9 ± 10.7</td>
<td>147.1 ± 21.6</td>
<td>82.3 ± 13.8</td>
</tr>
<tr>
<td>TG</td>
<td>52.5 ± 15.2</td>
<td>35 / 6</td>
<td>5/10/25/1</td>
<td>87.4 ± 18.4</td>
<td>69.6 ± 11.8</td>
<td>139.7 ± 19.0</td>
<td>78.9 ± 14.5</td>
</tr>
</tbody>
</table>

P Value: Not Significant for all parameters

BW (body weight), HR (heart rate), SBP (systolic blood pressure), DBP (diastolic blood pressure), MAP (mean arterial pressure), PG (Precalculated group), TG (titration group).
Increase in HR (Table 2) was seen in both groups after propofol injection. A maximum increase occurred at the 6 minute mark in the PG and 8 minute mark in the TG. However, these changes were not statistically significant. SBP, DBP and MAP decreased in both groups after propofol injection. This decrease was greatest at 2 minutes in the PG and 10 minutes in the TG. Decrease in SBP, DBP and MAP were more in PG compared to TG. This decrease was statistically significant at 2, 4 and 8 minutes for SBP and 2 and 4 minutes for DBP and MAP. The total number of patients who required vasopressors (epinephrine and/or Phenylephrine) was 14/43 PG and 5/41 in TG. This difference was statistically significant.

Table 2
Percentage change in Hemodynamic Parameters (Heart Rate, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Arterial Pressure) in precalculated v/s Titration Group

<table>
<thead>
<tr>
<th>Hemodynamics</th>
<th>PG</th>
<th>TG</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 minutes</td>
<td>5.9 +/- 15.6</td>
<td>5.4 +/- 19.4</td>
<td>0.64</td>
</tr>
<tr>
<td>4 minutes</td>
<td>12.9 +/- 21.3</td>
<td>8.2 +/- 20.3</td>
<td>0.54</td>
</tr>
<tr>
<td>6 minutes</td>
<td>13.8 +/- 25.6</td>
<td>11.1 +/- 28.0</td>
<td>0.92</td>
</tr>
<tr>
<td>8 minutes</td>
<td>12.4 +/- 28.3</td>
<td>13.9 +/- 20.2</td>
<td>0.24</td>
</tr>
<tr>
<td>10 minutes</td>
<td>6.6 +/- 20.4</td>
<td>7.8 +/- 18.2</td>
<td>0.79</td>
</tr>
<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 minutes</td>
<td>-21.2 +/- 13.8</td>
<td>-11.1 +/- 13.4*</td>
<td>0.00</td>
</tr>
<tr>
<td>4 minutes</td>
<td>-18.2 +/- 27.6</td>
<td>-9.1 +/- 17.9*</td>
<td>0.02</td>
</tr>
<tr>
<td>6 minutes</td>
<td>-13.1 +/- 25.4</td>
<td>-6.6 +/- 26.3</td>
<td>0.26</td>
</tr>
<tr>
<td>8 minutes</td>
<td>-16.9 +/- 24.8</td>
<td>-6.81 +/- 21.6*</td>
<td>0.05</td>
</tr>
<tr>
<td>10 minutes</td>
<td>-19.6 +/- 22.1</td>
<td>-11.9 +/- 17.5</td>
<td>0.08</td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 minutes</td>
<td>-16.5 +/- 22.07</td>
<td>-5.5 +/- 23.1*</td>
<td>0.02</td>
</tr>
<tr>
<td>4 minutes</td>
<td>-14.9 +/- 24.9</td>
<td>-3.9 +/- 21.3*</td>
<td>0.03</td>
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<tr>
<td>6 minutes</td>
<td>-7.0 +/- 27.9</td>
<td>-2.63 +/- 32.3</td>
<td>0.51</td>
</tr>
<tr>
<td>8 minutes</td>
<td>-11.01 +/- 24.6</td>
<td>-4.7 +/- 29.8</td>
<td>0.37</td>
</tr>
<tr>
<td>10 minutes</td>
<td>-15.2 +/- 23.3</td>
<td>-9.0 +/- 25.8</td>
<td>0.25</td>
</tr>
<tr>
<td>MAP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 minutes</td>
<td>-19.1 +/- 16.0</td>
<td>-8.4 +/- 17.2*</td>
<td>0.00</td>
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<tr>
<td>4 minutes</td>
<td>-16.9 +/- 24.1</td>
<td>-6.7 +/- 18.0*</td>
<td>0.01</td>
</tr>
<tr>
<td>6 minutes</td>
<td>-10.5 +/- 24.5</td>
<td>-5.0 +/- 26.9</td>
<td>0.34</td>
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</table>
EFFECT OF PROPOFOL TITRATION V/S BOLUS DURING INDUCTION OF ANESTHESIA ON HEMODYNAMICS AND BISPECTRAL INDEX

When the percentage difference in hemodynamic parameters (HR, SBP, DBP and MAP) from before intubation to immediately after intubation was compared between the two groups, PG showed increase in HR and decrease in SBP, DBP and MAP. TG had similar increase in HR, however, SBP, DBP and MAP also increased in them. Only the difference in DBP and MAP were statistically significant (Table 3).

<table>
<thead>
<tr>
<th></th>
<th>PG</th>
<th>TG</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in Heart Rate Before &amp;After Intubation</td>
<td>14.1 +/- 18.8</td>
<td>14.1 +/- 22.7</td>
<td>0.80</td>
</tr>
<tr>
<td>Changes in SBP Before &amp;After Intubation</td>
<td>-19.0 +/- 28.3</td>
<td>1.3 +/- 21.8</td>
<td>0.07</td>
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<tr>
<td>Changes in DBP Before &amp;After Intubation</td>
<td>-12.3 +/- 32.5</td>
<td>11.9 +/- 24.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Changes in MAP Before &amp;After Intubation</td>
<td>-15.6 +/- 30.2</td>
<td>6.4 +/- 19.9</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* p ≤0.05 v/s PG.

HR (heart rate), SBP (systolic blood pressure), DBP (diastolic blood pressure), MAP (mean arterial pressure), PG (Precalculated group), TG (titration group).

Mean induction dose of propofol (Fig. 1) in the TG was 122.4 mg. It was significantly lower (p <0.05) than the mean calculated propofol amount 174.9 mg if propofol was given in them based on bodyweight as 2 mg/kg similar to PG.
BIS decreased in both the groups immediately after injecting propofol. It had reduced from 94.2 at baseline to 46.2 after induction in PG and from 93.4 at baseline to 54.3 after induction in TG. In both the groups BIS remained around 50 at the time of intubation and at 10 minute mark. There was no significant difference in BIS at baseline, after propofol induction, at intubation, and at 10 minutes between two groups (Fig. 2).

Discussion

Induction with propofol is known to cause decrease in blood pressure. Studies have demonstrated up to a
28% decrease in SBP, an 11% decrease in MAP, and a 19% decrease in DBP. In our study, when propofol was administered as a 2 mg/kg IV bolus (PG), SBP decreased by 20%. There was also a decrease in DBP and MAP by 16% and 19%. In a recent study, Cheng et al. proposed a molecular pathway that may contribute to vasodilatory effect of Propofol. Due to the inhibitory effect of propofol on baroreflexes and sympathetic activity, the effect of propofol on heart rate is variable with many studies showing decrease in heart rate. In our study, we found an increase in heart rate following induction with propofol similar to a study by Robinson et al.

Several studies with varied methods of delivery have demonstrated reduced hemodynamic effects and a decrease in dose requirements of Propofol. Studies have also shown that a slower injection of Propofol decreases cardiovascular effects. However, slow injection may also result in longer induction times. In a recent study using a target controlled infusion, Liu et al. demonstrated that the decrease in SBP was significantly less when propofol was given in a step wise technique with an initial plasma concentration of 2.0 mg/ml and then raised to a target plasma concentration of 4.0 mg/ml. In a study evaluating a priming principle for Propofol, there was a decrease in dose requirement, and fewer hemodynamic side effects. Priming was accomplished by first giving 20% of the total calculated dose and then the remaining dose until loss of eyelid reflex.

In our study, we titrated propofol to clinical parameters with incremental doses of 10 mg every 3 seconds until loss of eyelid reflex and/or verbal response. We found that titration reduced the hemodynamic effects of propofol. All through 10 minutes, SBP, DBP, and MAP decreased in PG more compared to TG. Titration also resulted in a 30% reduction in dose requirement.

Laryngoscopy and tracheal intubation is known to increase sympathetic response and therefore result in hypertension. Following intubation, increase of MAP from 35 mmHg to 60 mmHg compared to preintubation values have been reported. One of the important factors which could contribute to increased sympathetic response is intubation provider himself. We wanted our study to be clinically oriented; hence tracheal intubation providers were different at different point of the study. This could have affected the hemodynamic response to intubation. To overcome this, we excluded from analysis all the patients who had difficult tracheal intubation requiring either multiple laryngoscopies or re-dosing of propofol. Earlier studies had shown that propofol even in high bolus doses up to 3.5 mg/kg or different rate of infusion did not modify hypertensive response to intubation. In our study, we found increase in blood pressure in TG, however in PG there was further decrease in SBP, DBP, and MAP after intubation compared to preintubation values. Administration of fentanyl and lidocaine might have attenuated the hypertensive response to intubation and thus decreasing the effect of intubation on hemodynamic changes.

Studies have confirmed the use of BIS monitoring as an objective marker for assessing level of consciousness. BIS index correlates with the magnitude of sedation and loss of consciousness. A BIS value of 40-60 is preferred for surgical patients. When we compared BIS in both PG and TG, we found no significant difference between the groups and TG was able to achieve same BIS in spite of low induction dose.

Our study was basically designed to mimic clinical practice as close as possible. Hence it is limited by many factors as we included most patients who presented to our clinic without exercising stringent inclusion criteria like ASA status or history of hypertension/cardiac disease etc. Tracheal Intubation providers were different for different patients and no changes were made with the clinical protocol of the patients like administration of other agents like Versed, fentanyl or lidocaine as all of these agents are routinely used for induction of anesthesia. In our study, all the patients in both the groups received these drugs.
Titration to clinical parameters is common among anaesthesia practitioners as nearly all drugs are titrated to an objective or subjective end point. Propofol titration is also a conventional method. However, it is our experience that it is very common practice to inject propofol as a bolus dose for induction. Our method of titrating propofol to clinical parameters with incremental dose is very simple, negates the need for extra equipment like an infusion pump and, is easy to clinically adapt.

In conclusion, titration of propofol with incremental increases reduces changes in blood pressure, induction dose requirement and is able to achieve same level of BIS as in bolus.
References


Abstract

**Background:** Correct placement of a laryngeal mask airway (LMA) requires confirmation to appreciate the adequacy of laryngeal seal and pulmonary ventilation.

**Objectives:** The present study was designed to assess the feasibility of ultrasound use for confirmation of correct placement of LMA and its correlation with fiberoptic laryngoscopy as a confirmation tool for LMA position.

**Materials and Methods:** 31 ASA I and II patients scheduled for same day surgery under general anesthesia underwent standard general anesthetic technique with AuraOnce™ or AuraFlex™ Disposable Laryngeal Mask Airways. The position of the LMA cuff was confirmed by transverse neck ultrasound (USG), and reconfirmed with intra-LMA fiberoptic laryngoscopy (FOL).

**Results:** The ultrasound grade of LMA position strongly correlated positively with the fiberoptic grade of LMA position (r=0.92; p<0.0001). This correlation was obtained immediately after LMA placement, as well as just before LMA removal. The Bland-Altman scatter plot showed insignificant differences between the two grading systems with small and good limits of agreement (-0.63 to +0.57).

**Conclusion:** Ultrasound examination can replace fiberoptic examination for confirmation of the correct placement of an LMA. Additionally, non-invasive ultrasound examination can further give insight into the cause of airway/ventilation events that may be interfering with the LMA placement and ventilation.

Introduction

Correct placement of a laryngeal mask airway (LMA) requires confirmation to appreciate the adequacy of laryngeal seal and pulmonary ventilation. This confirmation may help to diagnose the etiology of peri-operative airway and ventilation events associated with LMA placement. These events can be prevented by adjusting a malpositioned LMA under the direct guidance of confirmation tools. Campbell et al\(^1\) concluded that a
fiberoptic laryngoscope (FOL) acts as one such confirmation tool that assesses the adequacy of LMA position. They stressed that ideal intra-oral positioning of an LMA may be highly desirable wherein direct visualization by fiberoptic laryngoscopy may be a better confirmation tool compared to the blind, standard method. However, FOL may be invasive and requires tedious sterilization of the fiberoptic laryngoscope questioning the regular use of this confirmation tool for LMA placement.

The first reported use of ultrasound for confirmation of correct LMA positioning opens up a new avenue for the use of ultrasound in airway management by the anesthesiologists. The intra-oral LMA cuff may be distorted to varying degrees depending on the enormity of the epiglottis or pre-epiglottic space. Our hypothesis was that ultrasound will help us visualize and grade this distortion. Henceforth, the present study was designed to assess the feasibility of ultrasound use for confirmation of correct placement of LMA and its correlation with fiberoptic laryngoscopy as a confirmation tool for LMA position.

Materials and Methods

After institutional review board approval with waiver for written informed consent, a prospective clinical case series was conducted in 31 ASA I and II patients at an academic university hospital. Patients were aged 12-65 years, weighing 50-100 kgs, who were scheduled for same day surgery under general anesthesia. A standard general anesthetic technique was used. AuraOnce™ or AuraFlex™ Disposable Laryngeal Mask Airways (Ambu Inc., Glen Burnie, Maryland, United States) were placed with a standard technique, as recommended by the manufacturer.

The following observations were made:

The position of the LMA cuff was confirmed by transverse neck ultrasound (USG) per the grading in Table 1, and reconfirmed with intra-LMA fiberoptic laryngoscopy (FOL) per the grading in Table 2 (licensed use of the table from the Springer Publishers) as devised by Aoyama et al. The grading was repeated before removal of the LMA at the end of anesthesia so that change in LMA position if any could be recorded. The ultrasound examination was performed with a LOGIC® i ultrasound machine (GE Healthcare, Waukesha, Wisconsin, United States). Transverse ultrasound views of the LMA cuff were obtained with progressive transverse tilt of the 8L-RS linear array probe (4-12 MHz) as schematically shown with airway manikin in Fig. 1-3. Ultrasound grading was done in the transverse view obtained as per probe position in Fig. 3 wherein the linear ultrasound array is in complete alignment with the correctly placed intra-oral LMA cuff. Intra-LMA fiberoptic laryngoscopy was performed with an Olympus LF-GP tracheal intubation fiberscope (Olympus America Inc., Center Valley, Pennsylvania, United States).

Table 1
Grading score of ultrasound (USG) confirmation of laryngeal mask airway position

| Grading Score of USG: |  |
|----------------------|  |
| Grade 1              | Tent view of the LMA cuff |
| Grade 2              | Slight Indentation of the LMA cuff |
| Grade 3              | Gross Indentation of the LMA cuff |
| Grade 4              | No Tent view of LMA cuff |
| Grade 5              | Ventilation not adequate |

Table 2
Grading score of fiberoptic laryngoscope (FOL) confirmation of laryngeal mask airway position

Grading score of fiberoptic laryngoscope (FOL) confirmation of laryngeal mask airway position

284
Score of FOL as devised by Aoyama et al:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glottis completely visible while the epiglottis was not identified</td>
</tr>
<tr>
<td>2</td>
<td>Glottis slightly obscured by the tip of the epiglottis</td>
</tr>
<tr>
<td>3</td>
<td>More than half of the glottis obscured by the epiglottis</td>
</tr>
<tr>
<td>4</td>
<td>Glottis completely obscured by the epiglottis (complete downfolding)</td>
</tr>
<tr>
<td>5</td>
<td>Ventilation not adequate</td>
</tr>
</tbody>
</table>

*Fig. 1*

Progressive transverse tilt of ultrasound probe as schematically obtained with airway manikin-I

*Fig. 2*

Progressive transverse tilt of ultrasound probe as schematically obtained with airway manikin-II

*Fig. 3*

Progressive transverse tilt of ultrasound probe as schematically obtained with airway manikin-III
A Spearman’s rank correlation test was used to examine the strength and direction of correlation between the USG and FOL procedures, as ordered data. “Limits of agreement” with Bland-Altman Plot was used to further compare the two methods (USG and FOL grading). Intraoperative airway and ventilation events were recorded along with the frequency of the intraoperative LMA manipulations to maintain adequate ventilation.

**Results**

The ultrasound grade of LMA position strongly correlated positively with the fiberoptic grade of LMA position \((r = 0.92; \ p < 0.0001)\). This correlation was obtained immediately after LMA placement, as well as just before LMA removal. In one patient, the incidental diagnosis of an asymptomatic epiglottic growth was made with ultrasound that was reconfirmed with the fiberoptic laryngoscope; the epiglottic growth was a cause of failure of LMA placement on the first attempt and interfered with adequate ventilation. No airway or ventilation events occurred in any other patient. Although we had a relatively small number of patients, there was a significant effect correlation \((r = 0.92; \ p < 0.0001)\) between ultrasound and fiberoptic grades (Fig. 4). Additionally, the Bland-Altman scatter plot (Fig. 5) of the differences between the USG and FOL grading showed insignificant bias or difference between the two grades (near-zero mean: -0.03) with small limits of agreement (-0.63 to +0.57) and 90% of the plotted difference in grades were zero and scattered on x-axis \([y(Grades’ \ Difference) = 0]\).
Discussion

There has been a new push for utility of the ultrasound in upper airway management\textsuperscript{4,12}. The present study was designed to evaluate a possible use of the ultrasound for LMA placement. The working hypothesis was that when the LMA is correctly placed, the cuff of the LMA maintains its ‘reverse hanging drop’ contour inside the laryngopharynx\textsuperscript{13}. However, as the cranial half of the LMA cuff lies in the glossoepiglottic fold, this contour of
the cuff may be hard pressed upon by the weight of the large epiglottis or large amount of fat in the pre-
epiglottic space. This distortion in the LMA cuff may be varied depending on the enormity of the epiglottis or
pre-epiglottic space. Hence we hypothesized that ultrasound will help visualize the cranial half of the LMA cuff
and we graded the ultrasound views according to the distortion incurred on the cuff by the epiglottis/pre-
epiglottic space. The ultrasound views ranged from ‘tent’ view similar to the igloo tent as the normal contour
with minimal interference from the epiglottis/pre-epiglottic space, to the ‘no tent’ view with complete
obscuration from the epiglottis/pre-epiglottic space. We were able to correlate these ultrasound views with the
intra-LMA fiberoptic laryngoscope views because whether the epiglottis was large or the pre-epiglottic space
had a large amount of fat, the final result was the varying degrees of obstruction of the laryngeal inlet and
hence varying degrees of potential interference of adequate ventilation with the LMA. Because positive
pressure ventilation or spontaneous ventilatory efforts may reversibly and rhythmically move the epiglottis
cranio-caudally with each breath giving the anesthesiologist a false sense of security regarding the adequacy of
ventilation, the knowledge about varying degrees of obstruction of the laryngeal inlet can help the anesthesia
care provider to be cautious and alarmed about the potential airway obstruction during surgery or when the
LMA is removed after the surgery. As ultrasound non-invasively provides both reassuring views of LMA
placement as well as alarming views of possible laryngeal inlet obstruction, the anesthesiologists have an
additional tool of patient safety when providing anesthesia with an LMA.

When visualizing the structures and LMA with the ultrasound, the operator can sometimes confuse the
ultrasound image of the indentation of the LMA with the ultrasound image of the epiglottis; however this
confusing imaging can be easily overcome by deflating the cuff of the LMA. On deflation of the cuff, the
ultrasound image of the LMA will disappear while the ultrasound image of the epiglottis will persist.

The limitations to the study are: (a) extremely small number of subjects though the correlation was
significant; (b) the non-blinding of the fiberoptic grading and ultrasound grading between the observers who
graded the views though this was unavoidable due to logistic reasons; (c) logistical non-availability of the
stored (printed or electronic) ultrasound images to demonstrate the applied USG grading in the presented study
and (d) the seemingly apparent inadequacy to add more information by the fiberoptic grading (and/or additional
ultrasound grading) over the clinical assessment (by visual inspection, capnography and quality of airway seal)
for adequacy of LMA placement and ventilation. However, the non-invasiveness of ultrasound provides the
opportunity for examining the patient’s anatomical airway and its interaction with LMA-in-situ so that etio-
pathogenesis of the airway and ventilation parameter changes secondary to the LMA placement can be
understood, and individually corrected per se with adjustments of the LMA position under the direct and real-
time visualization with ultrasound without the need for the tedious fiberoptic guidance.

Conclusion

Ultrasound examination can replace fiberoptic examination for confirmation of the correct
placement of an LMA. Ultrasound examination is non-invasive, less tedious and can be done
repeatedly without any interruption in ventilation because each fiberoptic examination involves
insignificant but minimal interruption of the ventilation during the time period of examination.
Finally, ultrasound examination can further give insight into the cause of airway/ventilation
events that may be interfering with the LMA placement and ventilation.
Acknowledgement

The authors deeply appreciate and are thankful to Dr Ronald Thomas, Children’s Research Center of Michigan, Wayne State University and Dr George McKelvey, Post-Doctoral Fellow, Anesthesiology, Wayne State University, for completing the statistical analysis for the study. The authors are also thankful to Dr Elie Chidiac, Anesthesiology Residency Program Director, Wayne State University for reviewing and correcting the final manuscript before the submission.
References

ANESTHETIC MANAGEMENT OF A MORBIDLY OBESE PARTURIENT UNDERGOING CESAREAN SECTION

HANAN EL SHOBAKY*, IAN KAUFMAN* AND THOMAS SCHRICKER**

Introduction

Obesity has reached an epidemic proportion globally with a comparable rise in prevalence among women in the reproductive age. Not surprisingly, the number of obese parturients has more than doubled in the last 10 years.

Obesity per se has been identified as a significant risk factor for respiratory and infectious complications in general surgery and for anaesthesia related mortality in obstetrics. When compared to normal weight parturients obese patients are at increased risk of having either concurrent medical problems or superimposed antenatal diseases including pre-eclampsia and gestational diabetes. Complications during labor such as intrapartum fetal distress, failure to progress, abnormal presentation necessitating instrumental delivery and cesarean section are more common. In addition there is an increased incidence of deep vein thrombosis, hypoxemia, and wound infections perioperatively. Furthermore, the anaesthetist frequently has to deal with technical difficulties regarding airway management and regional anesthesia.

This case report of a morbidly obese parturient undergoing cesarean section highlights the complexity and challenges that are associated with the anaesthetic and obstetric surgical care of this patient population.

Case report

We assessed this 42-year-old Afro-American woman, G2 P0 at 30 weeks of gestation. The patient’s body weight was 187 kg and her body height was 160 cm (body mass index = 73 kg/m²). She had a history of obstructive sleep apnea, asthma, type 2 diabetes mellitus, and depression. Her medications included inhaled ventolin and flovent, and subcutaneous insulin. The patient’s airway appeared unremarkable (Mallampati II, thyromental distance >6 cm) and venous access looked obtainable. Typical anatomical landmarks of the spine were not palpable. Her oxygen saturation was 96% on room air, her echocardiogram showed normal cardiac function with a left ventricular ejection fraction of 65%. Following multidisciplinary discussions involving the obstetrician, anesthesiologist and neonatologist, the plan was made to attempt vaginal delivery under epidural analgesia initiated at an early stage of labour, and, if needed, to perform cesarean section under epidural anesthesia in an operating theatre equipped for bariatric surgery.

At 39 weeks gestation, the patient was admitted for induction of labour. Two anesthetists prepared the

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patient for epidural catheter insertion. They placed the patient in the sitting position and retracted the fat pads on her back from the midline using adhesive taps as described elsewhere\textsuperscript{10}. A 22G Whitacre needle was used to delineate the spinous processes above and below the interspace, presumably at L1/L2. Verbal communication with the patient was used to identify the midline. Using a 12.5 cm Touhy needle the epidural space was located without difficulty at 7.5 cm and the epidural catheter was advanced 7 cm. Following the administration of a test dose of 3 ml lidocaine 2\%, a bolus of 25 mg bupivacaine was injected in increments of 5 mg. Continuous epidural infusion of 0.06\% bupivacaine with 2 μg/ml fentanyl was started at a rate of 12 ml/h resulting in satisfactory pain control.

After 22 hours failure to progress at 7 cm cervical dilatation prompted the decision to proceed with surgical delivery. The patient was transferred to the operating room and secured on the operating table in the ramped position with a slight left lateral tilt (Fig. 1). She received 30 ml sodium citrate \textit{per os} to lower gastric acidity. Five L/min oxygen was delivered via nasal prongs. Two 16G intravenous catheter were inserted together with a 20G intra-arterial catheter for continuous pressure monitoring. After the intravenous administration of 1000 ml NaCl (0.9\%), a total of 15 ml lidocaine 2\% with epinephrine 1/200000 were given in the epidural catheter in increments of 5 ml leading to a confirmed bilateral sensory block to the T3 dermatome. Blood pressure was maintained within normal values by continuous infusion of phenylephrine at 500 μg/h, intravenous colloid (1000 ml Pentaspan\textsuperscript{®} , Bristol-Myers Squibb, Canada) and NaCl 0.9\% (1000 ml). The help of four operating room attendants was required to retract the patient’s abdominal pannus cephalad to facilitate a horizontal lower segment incision (Fig. 2, 3, 4). A 30° Trendelenburg position was established to improve surgical exposure with little discomfort for the patient. It took a total of 55 min to adequately prepare the patient for surgical skin incision.
Fig. 1

The patient in the ramped position before retraction of the abdominal pannus
Fig. 2
The abdominal pannus retracted manually by the surgeon to expose the incision landmarks.
Fig. 3

The abdominal pannus retracted cephalad
Fig. 4

The patient position after retraction of the pannus during surgery
Blood gas analysis was unremarkable (pH: 7.32, pCO$_2$: 37 mmHg, pO$_2$: 114 mmHg, SaO$_2$: 98%). The patient’s oxygen saturation was maintained 98-99% throughout the procedure. Intravenous boluses midazolam 0.5 mg, fentanyl 25 μg and ketamine 20 mg were given to decrease the patient’s anxiety.

Sixty minutes after skin incision, ventouse application to deliver the baby failed followed by a hypercontracting uterus necessitating the administration of sublingual nitroglycerine. A viable healthy looking baby was delivered by forceps (male, 4,295 grams, APGAR scores 8 and 9). Subsequently intravenous boluses of midazolam 1 mg, ketamine 40 mg, and fentanyl 25 μg were given. In addition two epidural boluses of 5 ml bupivacaine 0.25% were administered together with 3 mg morphine. Oxytocin infusion was started at 100 U/liter and decreased to 50U/liter later resulting in a total intraoperative dose of 250U. CarboProst tromethamine (Hemabate®) 250 μg was injected directly into the uterus. Ticarcillin and clavulanate (Timentin®) 3.1 gm, ampicillin 1g and heparin 5000U were given. The uterine cavity was closed three hours after skin incision and excellent haemeostasis was obtained. Estimated blood loss was 750 ml.

Prior to closure of the peritoneum, suspicious odour led to the diagnosis of a perforated sigmoid colon. Primary repair was performed by a general surgeon who requested complete surgical muscle relaxation for this procedure. Thus, general anesthesia had to be induced. Following airway topicalisation using a technique described by our group previously we performed an awake fiberoptic intubation followed by general anesthesia using inhaled sevoflurane and muscle paralysis using rocuronium. After completion of this surgical procedure which lasted another three hours the patient was transferred to the ICU intubated. She was ventilated for 22 hours and the postoperative course was uneventful. Mother and son left the hospital on postoperative day 13.

**Discussion**

Morbid obesity accentuates the physiological changes associated with pregnancy. It is not uncommon in the morbidly obese parturient to see systolic and diastolic dysfunction of the left ventricle, pulmonary hypertension and obstructive sleep apnea. Endothelial dysfunction, a consequence of insulin resistance and dyslipidemias, may predispose these patients to pregnancy induced hypertension. The supine hypotension syndrome associated with pregnancy can be greatly exaggerated because the large panniculus adds to the uterine compression of the vasculature. Not surprisingly there are case reports of sudden death in morbidly obese pregnant patients on assuming the supine position. Prevalence and severity of gastric reflux are increased in the morbidly obese leading to an increased risk of aspiration during anesthesia. As the anesthetic and surgical care of the morbidly obese parturient is challenging; early and meticulous multidisciplinary planning involving senior anesthesiologists, surgeons, nurses and the procurement of special equipment is mandatory.

When this patient was seen by a senior obstetric anesthesiologist at 35 weeks gestation a multidisciplinary team approach was formulated. Although surgical delivery is very likely in the morbidly obese parturient, the primary obstetric plan was to induce labour and to attempt vaginal delivery. The anesthesiologist’s main concern was to avoid an emergency situation requiring urgent endotracheal intubation.

Notwithstanding the technical difficulties associated with regional anesthesia in the morbidly obese such as patient positioning, identification of anatomical landmarks, and more frequent dislodgment of epidural catheters, its successful use for cesarean section has been reported. Epidural anesthesia offers several advantages.
advantages, including an easily titratable local anesthetic dose and level of anaesthesia, ability to extend the block for surgical delivery and prolonged surgery, slower and more easily controllable hemodynamic changes, decreased potential for excess motor blockade and its utilization for postoperative analgesia.\textsuperscript{22,23}

We therefore opted to place an epidural catheter before induction of labour.

Probing the subcutaneous tissue and delineating the position of a posterior spinal process above and below a lumbar interspace with a 22-G 8.5 cm Whitacre needle while infiltrating a generous dose of local anesthetic,\textsuperscript{24} as well as verbal communication with the parturient to direct the needle to midline were instrumental for the successful placement of the epidural catheter in this patient.\textsuperscript{10} The epidural space was reached at 7.5 cm which is in agreement with other reports in morbidly obese subjects demonstrating that it is rarely deeper than 8 cm in this patient population.\textsuperscript{25,26}

As the presence of epidural fat and increased venous distension from aortocaval compression increases the cephalad spread of epidural local anesthetic the risk of hypotension and respiratory embarrassment is greater when compared to the lean parturient.\textsuperscript{22} In addition surgical retraction of a large panniculus further accentuates the cardiovascular compromise associated with neuraxial regional blockade.\textsuperscript{27}

When preparing for the cesarean section we inserted two large bore intravenous cannulas and an intrarterial catheter for continuous blood pressure measurement and blood gas analysis because obese parturient are at increased risk of bleeding and hypoxemia.\textsuperscript{8,9,10}

Although we carefully titrated the dose of epidural local anesthetic the injection of three boluses of 5 ml lidocaine 2\% led to a fall in systemic blood pressure requiring continuous vasopressor support and fluid resuscitation.

Both pregnancy and obesity increase oxygen consumption and CO\textsubscript{2} production. The stimulated metabolic demand together with limited chest wall compliance increases the work of breathing and decreases respiratory reserve. Supine and Trendelenburg position can cause the patient’s functional residual capacity (FRC) to fall below closing capacity resulting in small airway collapse, atelectasis, ventilation perfusion mismatch and hypoxemia.\textsuperscript{28} Supine position in the presence of regional anesthesia, especially when the block extends beyond the umbilicus, may, thus, provoke respiratory and cardiovascular failure if the patient’s cardiac reserve is compromised.\textsuperscript{29} On the other hand, pregnancy has been shown to improve FRC in obese subjects because increased plasma levels of progesterone enhance the brainstem’s sensitivity to CO\textsubscript{2} and directly promote lower airway dilatation, thereby counteracting the negative effects of obesity on the respiratory system.\textsuperscript{12} In the present case neuraxial blockade to T3 combined with the cephalad retraction of the abdominal panniculus did not result in respiratory dysfunction as reflected by normal pO\textsubscript{2} and pCO\textsubscript{2} values.

In morbidly obese patients the abdominal wall anatomy is distorted by the large panniculus. Hence, the type of the incision for cesarean section is critical to gain optimal surgical access. The proposed benefits of a transverse incision are a more secure closure, less fat dissection and pain facilitating earlier ambulation and breathing in the postoperative period.\textsuperscript{30} The disadvantage of a low transverse incision is an increased risk of infection. Vertical skin incision allows for better visualization of the operative field, but is associated with greater postoperative pain, a greater likelihood of wound dehiscence and hernia formation.\textsuperscript{30} In severe cases surgical panniculectomy prior to delivering the baby may be considered to facilitate access to the pelvis.\textsuperscript{31,33} Some obstetricians favor a midline supraumbilical or transverse incision above the pannus as the abdominal wall is often thinner above the umbilicus.\textsuperscript{34} In the present case the horizontal incision as well as the huge size and weight of the abdominal pannus made only the cephalad suspension feasible. Considering the long time
interval between establishing anesthesia and the uterine incision the avoidance of a prolonged exposure to general anesthetics during the preparation period proved useful and certainly contributed to the excellent APGAR values of the newborn.

Although the patient’s airway appeared to be unremarkable several factors prompted us to perform an awake fiberoptic intubation when surgical muscle paralysis was required to repair the bowel. Firstly the confidential inquiry into maternal deaths lists obesity as a major risk factor for failed intubation and aspiration of gastric contents at induction of anesthesia. The physiological and anatomical changes caused by both obesity and pregnancy increase the potential of an unanticipated difficult airway, impossible mask ventilation and rapid desaturation during the apneic phase. This risk of hypoxaemia was accentuated by the cephalad retraction of the pannus and a further reduced FRC. In addition, the prolonged Trendelenburg position could have induced or worsened a preexisting airway edema. Moreover, the surgery had been already started, which imposed limitations with respect to positioning the patient’s head for intubation.

Morbidly obese patients undergoing open abdominal surgery are at increased risk for serious respiratory complications including pulmonary embolism, pneumonia, atelectasis, aspiration and respiratory failure. These problems are directly related to the obese condition, and/or to co-morbidities such as obstructive sleep apnea. Hence, in our view it was mandatory to keep this patient on a ventilator and continue invasive monitoring in an intensive care setting postoperatively.

**Conclusion**

Successful management of the morbidly obese parturient requires a multidisciplinary team approach initiated early in pregnancy. Abdominal pannus retraction strategies include the preoperative consultation of bariatric and plastic surgery services and the consideration of the risks and benefits of upper versus lower segment cesarean section. Epidural anesthesia is an option for cesarean section. If general anesthesia is required the airway should be secured awake by using fiberoptic bronchoscopy ideally performed by an experienced endoscopist.
References


ANAESTHETIC MANAGEMENT OF A MORBIDLY OBESE PARTURIENT UNDERGOING CESAREAN SECTION


THE ADMINISTRATION OF GENERAL ANESTHESIA TO A PATIENT WITH CROUP

Gabriel Man*, Elizabeth Roman** and Steven M. Neustein***

Abstract

Croup in a young child may lead to severe airway narrowing, and would present a severe risk for administration of anesthesia. To the best of our knowledge, there have been no previous case reports of patients undergoing general anesthesia with croup. In our report, we describe a case of a 31 month old child with croup who required anesthesia.

Case Report

The patient was a 14 kg, 31 month old male who a recent diagnosis of T-myeloid mixed phenotype acute leukemia who presented to the ER with a distended abdomen, fatigue, and weight loss. He was noted to have abdominal mass and diffuse lymphadenopathy. A CBC was remarkable for WBC 399 K/mcL, Hgb 5.2 g/dL, platelet 144 K/mcL. Peripheral blood for flow cytometry and a bone marrow aspirate demonstrated T-lymphoblastic leukemia; additionally, a population of monocytic blasts were documented on the bone marrow. The patient underwent leukopheresis for three days and was enrolled on the Children’s Oncology Group AALL0434. After four weeks of chemotherapy, with 20-30% lymphoblasts in the bone marrow, the patient was an induction failure. In preparation for reinduction chemotherapy, a lumbar puncture was performed with intrathecal cytarabine. Despite having three prior atraumatic lumbar punctures with WBC \( \leq 1 \) and intrathecal methotrexate, including one the week before, the CSF demonstrated WBC 66 and RBC 1. A repeat lumbar puncture was critical to obtain more fluid to determine whether this was CNS disease developing on chemotherapy, which would profoundly influence the treatment regimen by requiring CNS radiation and also to give another triple intrathecal with methotrexate, cytarabine and hydrocortisone.

He was scheduled to undergo a diagnostic lumbar puncture and had previously successfully undergone multiple procedures with propofol sedation. Three days prior to the procedure, the patient was noted to be febrile (temperature 39°C) and coughing. His physical exam was significant for striderous breathing. Parainfluenza virus type3 was detected in nasopharyngeal secretions. He required one dose of racemic epinephrine on the 2nd day of illness. His WBC count was 8800. Soft tissue radiographs of the neck, taken 4 days and 1 day prior to the procedure, showed clear evidence of a narrowed airway (Fig. 1).

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Fig. 1
Chest x ray. Severe airway narrowing can be seen as a steeple sign.

The patient was brought to the holding area. His physical exam was significant for striderous breathing and a cushingoid appearance.

After a lengthy discussion with the oncology team and the family, the decision was made to proceed with the procedure due to the urgency of the patient’s condition.
Upon arrival in the room, the patient’s in situ Port-a-cath was accessed in a sterile fashion. He was sedated with 2 mg of midazolam. 0.1 mg of glycopyrrolate was administered to decrease secretions in the airway. Standard ASA monitors were attached to the patient and the patient was placed in the left lateral decubitus position. 20 mg of propofol was administered to the patient, but the breathing immediately became more striderous. Anesthesia was maintained with 4% sevoflurane and 5 cm H2O CPAP was administered by adjusting the APL valve on the circuit with manual assisted ventilation. The oncology team was able to successfully collect the CSF sample and administer the chemotherapy. Throughout the procedure, the patient maintained his oxygen saturation around 95% and did well post-operatively.

Discussion

Croup is a commonly occurring upper respiratory infection (URI) in the pediatric population. It is characterized by the presence of inspiratory stridor, a barking cough, and hoarseness. It is often caused by parainfluenza virus type 3. The narrowing of the airway is due to edema and erythema of the lateral walls of the trachea just below the vocal cord, caused by the infiltration of inflammatory cells into the lamina propria, submucosa, and adventitia. This results in a hypersensitive airway that only begins to resolve around 2 weeks after peak symptoms. It is commonly recommended that patients wait 4 weeks after the peak of their symptoms before undergoing general anesthesia for elective surgery.

In our case, the urgency of the patient’s condition, we were forced to weigh the risk and benefits of the situation. The administration of general anesthesia to patients with URIs has been associated with an increased incidence of adverse respiratory events, such as bronchospasm, laryngospasm, breath-holding, arterial desaturation, bacterial pneumonia, reintubation, and unanticipated hospital admission. The urgency of determining the patient’s chemotherapy progress was more important than the risks of undergoing general anesthesia. Thus, the decision was made to optimize the patient to undergo general anesthesia for the procedure.

It has been demonstrated in multiple studies that endotracheal intubation is an independent risk factor for developing laryngospasm and should be avoided. Fortunately in this case, a facemask was appropriate. The patient was administered glycopyrrolate to decrease secretions. Copious secretions have been shown to be an independent risk factor for developing adverse respiratory events. Studies have also shown that airway resistance is decreased by the administration of propofol. Sevoflurane has is known to be the least irritating to the upper airway reflexes. The most secure airway, the endotracheal tube, was to be avoided because it was associated with more respiratory complications.

The use of helium oxygen (heliox) may have been helpful in the administration of anesthesia. Turbulent flow is a common feature of a narrowed airway. Resistance increases in proportion to gas flow and density. The lower density of heliox, compared to air, helps to improve flow across the narrowed opening by decreasing resistance. However, this was not available to us. Furthermore, its role in the treatment of patients with croup remains a point of controversy. A recent study showed that it was no better than racemic epinephrine in the treatment of croup.

Therefore, by tailoring our anesthesia, we were able to successfully administer general anesthesia to a pediatric patient with an active croup infection, without adverse respiratory events.
References

INTRAOPERATIVE CORONARY ARTERY VASOSPASM: A TWIST IN THE TALE!

MICHAEL S. GREEN, D.O. AND SHELDON GOMES, MD

Abstract

The cause of variant angina is localized hyperresponsiveness of the vascular smooth muscle cells caused by non-specific stimuli of vasoconstriction. Autonomic imbalance can be one of the mechanisms of spontaneous vasospasm, and sympathetic or parasympathetic stimulation can induce Coronary Artery Spasm (CAS). Although various reports of CAS events have been described, episodes associated with untwisting or manipulation of a visceral structure remains unique. We report one such case of CAS in association with intraoperative untwisting of a torted ovarian cyst treated with intracoronary nitroglycerine in the catheterization laboratory.

Vasospastic or variant angina is a well known clinical condition first described by Prinzmetal and colleagues, characterized by CAS in normal and diseased coronary arteries. General anesthesia can be a triggering event. This case demonstrates unique etiology in that spasm was provoked by surgical manipulation of a torted ovarian cyst. CAS has been implicated as a cause of sudden, unexpected circulatory collapse and death during surgery, cardiopulmonary bypass, and other non-cardiac surgical procedures. There are few reports of coronary vasospasm during regional anesthesia and neuroaxial block.

Many factors are involved in the occurrences of perioperative CAS including activated sympathetic activity, activated parasympathetic activity, cocaine, alkalosis, hypercalcemia, magnesium deficiency, succinylcholine, vasopressors, essential hypertension, Hyperthyroidism, epidural anesthesia, spinal anesthesia, smoking, lipid metabolic disorder, coronary artery aneurysm, commercial weight loss products.

We describe a rare case of CAS during general anesthesia, in a patient with no past history of coronary artery disease, possibly provoked by surgical manipulation of a torted ovarian cyst, which was diagnosed and treated promptly via cardiac catheterization.

Intraoperative coronary artery vasospasm: a twist in the tale!

Introduction

Vasospastic or variant angina is a well-known clinical condition first described by Prinzmetal and colleagues and is characterized by coronary artery spasm (CAS), which may occur in angiographically normal and diseased coronary arteries. If not effectively treated, CAS complications include acute myocardial
infarction, life-threatening dysrhythmias, and death. Because of its sudden onset and its ability to mimic obstructive coronary ischemia, CAS is difficult to diagnose during general anesthesia.

The cause of variant angina is localized hyperresponsiveness of the vascular smooth muscle cells caused by non-specific stimuli of vasoconstriction\(^2\). Autonomic imbalance can be one of the mechanisms of spontaneous vasospasm, and sympathetic or parasympathetic stimulation can induce CAS\(^2-7\). Although various reports of CAS events have been described, literature search did not reveal episodes associated with untwisting or manipulation of a visceral structure. We report one such case of CAS in association with intraoperative untwisting of a torted ovarian cyst.

**Case report**

A 36-year-old Caucasian female, 5 feet 11 inches, 260 pounds, presented to the emergency department with a 2 day history of left lower quadrant pain. Ciprofloxacin treatment from her primary care physician for 24 hours with no improvement preceded presentation. On admission the pain was severe (10/10), sharp, constant, and radiating to her back and vagina.

Asthma, hypertension treated with enalapril 2.5 mg once daily, and 15 pack-year smoking defined past medical history. She had no prior history of ischemic heart disease. Past surgical history included a cholecystectomy and cesarean section. A negative history of sexually transmitted diseases and being multiparous were other pertinent findings. She had no allergies and no other medications.

Her initial vital signs were stable with temperature of 98.5 degrees, heart rate 88 beats per minute, blood pressure 150/92 mmHg, and respiratory rate 16 breaths per minute. Tenderness to deep palpation in the left lower quadrant persisted with vaginal examination revealing cervical motion tenderness and bilateral adnexal tenderness. Ultrasound and CT scan discovered a complex, cystic, 10.3 × 13 × 13 cm left adnexal mass. Lab findings were unremarkable and urine pregnancy test was negative. She was admitted to the gynecology service and started on Cefotetan 2g q12h and Doxycycline 100 mg q12h and scheduled for a diagnostic laparoscopy. Pre-operative EKG showed no evidence of ischemia (Fig. 1).
On day 3 of her hospital stay she underwent a diagnostic laparoscopy with general anesthesia. Rapid sequence induction using propofol 200 mg and suxamethonium 120 mg facilitated securing of the airway with a size 7.0 oral endotracheal tube. No instability was noted on induction. Desflurane maintained general anesthesia. Intravenous fentanyl provided analgesia and cisatracurium provided muscle relaxation. Laparoscopy revealed the left ovarian mass was torsed 3 times. Forty-five minutes following initial incision the ovary was untwisted. At this point significant ST elevation was noted on the telemetry monitor in association with a drop in systolic blood pressure from 120 mmHg to 80 mmHg and hypoxemia. Subsequent 12 lead EKG revealed significant ST elevation in LII, LIII, and aVF with ST depression in V1-4 suggestive of acute inferior-posterior myocardial infarction. (Fig. 2) Arterial blood gas analysis showed pH: 7.33, pCO2:55, pO2:69, HCO3:29, BE:+2, Na:138 mmol/L, K:3.5 mmol/L, Glu:138 mg/dL, Ca:1.1, Hb:13.6 g/dL. The patient was treated with 100% O2, crushed aspirin 325 mg via orogastric tube and boluses of Ephedrine and Phenylinephrine, 30 mg and 300 mcg respectively, in divided doses. A left salpingo-oophorectomy was completed expeditiously. Interventional cardiology was consulted and the patient was transferred to the cardiac catheterization lab within 25 minutes from the onset of EKG changes under propofol anesthesia.
The patient underwent emergent cardiac catheterization and coronary angiography via the right femoral artery. The right coronary artery (RCA) was a large caliber dominant vessel. Irregular and moderate stenosis was present in the proximal to mid RCA which resolved completely after injection of intra-coronary nitroglycerin. A large RCA with no evidence of acute lesion or thrombus remained, consistent with coronary spasm. Left ventricular function was preserved and pulmonary capillary wedge pressure was normal. No obvious pulmonary embolus was demonstrated on pulmonary arteriogram.

The patient was transferred to the Cardiac Care Unit (CCU) from the cardiac catheterization lab and extubated 5 hours post operatively. Subsequent Troponin studies were mildly elevated on postoperative day 1. She was discharged home on post operative day 3, with no sequelae, treated with a calcium channel blocker and nitrate. Pathology subsequently revealed a serous cystadenoma with no evidence of carcinoma.

**Discussion**

Vasospastic or variant angina is a well known clinical condition first described by prinzmetal and
INTRAOPERATIVE CORONARY ARTERY VASOSPASM: A TWIST IN THE TALE!

colleagues, characterized by coronary artery spasm in normal and diseased coronary arteries. CAS is more prevalent in the Japanese than Caucasian population. Typical EKG changes include sudden ST segment elevation in the leads overlying the ischemic region with associated ST segment depression in the reciprocal leads. The resolution phase of coronary spasm is characterized by rapid return to baseline of ST segments.

General anesthesia can be a triggering event although CAS during anesthesia is rare. This case demonstrates unique etiology in that the CAS was provoked by surgical manipulation of a torted ovarian cyst. CAS has been implicated as a cause of sudden, unexpected circulatory collapse and death during surgery, cardiopulmonary bypass, and other non-cardiac surgical procedures. There are few reports of coronary vasospasm during regional anesthesia and neuroaxial block.

Known risk factors for CAS include cigarette smoking, which this patient had, and lipid metabolic disorders. These predisposing factors may contribute to vascular endothelial dysfunction manifested as a propensity to spasm. At the cellular level, this coronary artery hypercontractility has been attributed to a reduced bioavailability of nitric oxide, up-regulation of Rho-kinase, and excessive levels of high-sensitivity C-reactive protein in the region of arterial spasm.

The cause of perioperative CAS is unknown. Many factors are involved in the occurrences of perioperative CAS including activated sympathetic activity, activated parasympathetic activity, cocaine, alkalosis, hypercalcemia, magnesium deficiency, succinylcholine, vasopressors, essential hypertension, Hyperthyroidism, epidural anesthesia, spinal anesthesia, smoking, lipid metabolic disorder, coronary artery aneurysm, commercial weight loss products.

Potential general mechanisms to explain the occurrence of coronary vasospasm in this subset of patients include redistribution of blood flow, altered humoral factors, increased catecholamine response secondary to the level of anesthesia, and imbalance of vasoconstrictor-vasodilator forces. More specific factors thought to provoke spasm may interact in the perioperative period, including increases in blood pH, excess α-adrenergic activity, stimulation of the parasympathetic nervous system, physical manipulation of a coronary artery, and release of vasoconstrictor substances by platelets.

Disruption of the sympathetic-parasympathetic balance has been theorized as a cause of vasospasm. Stimulation of the parasympathetic nervous system or acetylcholine administration may contribute to the genesis of the CAS. This causal relationship has been demonstrated in numerous studies. Acetylcholine is one of the alternatives (such as histamine, dopamine, serotonin, or hyperventilation) to ergonovine, an ergot alkaloid, which is used to stimulate α-adrenergic and serotonin receptors to specifically provoke vasospasm.

Vagal afferents innervate a diverse range of structures of the thoracic and abdominal viscera. A proportion of these afferents function as mechanoreceptors and respond to changes in intramural tension within the structures innervated. Mechanosensitive visceral afferent input is well represented in literature in terms of the genesis of vagal reflexes. In this patient, untwisting of the torted ovarian cyst may have resulted in such an autonomic imbalance which triggered CAS.

Prompt coronary angiography, as in this case, is the only definitive modality for early diagnosis and targeted treatment. Pharmacological testing, such as provocation with intravenous ergonovine, should be used only under special conditions and with extreme care. The response of our patient to intra-coronary nitroglycerin was dramatic. If transfer to the cardiac catheterization lab is delayed, intravenous nitroglycerine has also been reported to reverse intraoperative CAS. However, intravenously administered nitroglycerin is not always effective. Nifedipine, a calcium-channel blocker, is effective in relieving coronary artery spasm. Unlike
nitrates, nifedipine prevents smooth muscle contraction by inhibiting the inward calcium current during depolarization, thereby preventing excitation contraction coupling. Nifedipine may be used if CAS is refractory to nitrates. In cases with a high incidence of suspicion, a preoperative calcium-channel blocker should be administered, and nitroglycerin should be available during surgery.

In conclusion, we have described a rare case of CAS during general anesthesia, in a patient with no past history of coronary artery disease, possibly provoked by surgical manipulation of a torted ovarian cyst, which was diagnosed and treated promptly. Excellent interdisciplinary cooperation combined with favorable timing made this outcome possible without complications.
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DECEPTIVE LEVEL AFTER INTRATHECAL BLOCK FOR CESAREAN SECTION IN A PATIENT WITH PRIOR ABDOMINOPLASTY

A Case Report

AHMED ASSAS*, ETHAN O. BRYSON**, ELIZABETH A.M. FROST***

Abstract

Abdominoplasty is performed in an increasing number of patients, both male and female. The removal and hence rearrangement of abdominal skin may make assessment of the dermatome level of a subarachnoid block difficult. Also patients may hesitate, or even forget, to reveal cosmetic surgeries during the preanesthetic interview. Therefore it is important to maintain a high index of suspicion in patients who have had bariatric surgery. In this report we present the case of a deceptive anesthetic level in a parturient with an undisclosed history of abdominoplasty who presented for Cesarean section.

Introduction

In 1898, August Bier performed the first planned spinal anesthetic using cocaine to a 34 year-old laborer1. Neuraxial anesthesia for labor and delivery has progressed greatly since then and is now considered the standard of care for pain relief. However, accurate block level assessment continues to be a challenge. Cold, pinprick, and touch discrimination are conventionally used to determine the level of sensory block during spinal anesthesia. These tests have the advantages of being simple, repeatable, generally reproducible and applicable. Yet, their ability to accurately predict surgical anesthesia has been questioned. Furthermore, patient factors can contribute to the inaccuracy of these test results despite appropriate test administration by the clinician.

It is widely accepted that sensory block to the T4/T5 dermatome level is needed to provide adequate anesthesia for Cesarean section2. A block at this level is essential to provide adequate surgical anesthesia to include the visceral organs such as the uterus and the majority of the peritoneum. Identifying clinical situations that may lead to false test results and an understanding of the difference in testing modalities, can improve the accuracy of anesthetic level assessment.

Case Description

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A 32 year-old primipara presented for elective Cesarean section for breach presentation. Her past medical history included gastric bypass surgery that was performed 6 years prior resulting in a 42-kg weight loss. The patient denied any other medical or surgical history. After attachment of standard monitors, the patient was placed in the sitting position. A spinal anesthetic was performed at the L2-L3 level, using a 27g Whitacre needle. After confirmation of needle tip position by observation of cerebrospinal fluid flow, hyperbaric bupivacaine 0.75% 1.5 ml and preservative-free morphine 0.25 mg were administered intrathecally. The patient was then immediately placed in the supine position with left uterine displacement. Mild hypotension was treated with ephedrine. Anesthetic level assessment was tested by pinprick and measured at the T11 dermatome level bilaterally. The patient was then placed in slight Trendelenberg position to facilitate the spread of local anesthetic. Reassessment several minutes later indicated no rise in dermatome block level. Upon close physical examination of the patient’s abdomen, scarring suggestive of abdominoplasty was noted and the patient was questioned again regarding her surgical history. Though not otherwise noted in the medical record or discussed during the initial pre-operative assessment, the patient admitted that she had undergone extensive plastic surgery after her gastric bypass operation 5 years previously. She had failed to mention it earlier because she did not think that plastic surgery counted as “real” surgery. With this information, we again attempted to determine the level of anesthetic using the pinprick technique, testing posterolaterally beyond the area of abdominoplasty and appreciated a block level at T5.

The patient retained sensation to the anterior abdominal skin that had been pulled down low across her abdomen during the abdominoplasty but which corresponded to higher level dermatomes not reached by the spinal anesthesia. Realizing that administering more drugs intrathecally might result in cardiorespiratory compromise, we asked the obstetricians to use local anesthesia to eliminate sensation to this area or make the incision below the abdominal scar. The surgeons chose to incise below the abdominal scar in the area of skin corresponding to the original dermatomal anatomy where the spinal anesthesia had effectively rendered the patient insensate. An uneventful operation was performed. The patient did not report any unusual painful sensations throughout the course of delivery, indicating good visceral block.

Discussion

The most common modalities used to assess the spread of spinal anesthesia are cold, sharp pinprick and light touch. There is a wide variability between methods of assessing the level of the block, the reproducibility of these methods between clinicians, and the modality used. The issue is further complicated by the fact that there is no constant relationship between the levels assessed by these three sensory modalities. For example, Russell et al \(^3\) pointed out that the dermatome level at which sensitivity to cold is lost is usually higher than that of loss of sensation to pinprick, which in turn is higher than that of loss of sensation to light touch following spinal anesthesia. Additionally, loss of sensation to cold occurs before pinprick, and both of these are lost before loss of sensation to light touch is appreciated, as each stimulus is carried by different fibers (C, Ad and Ab fibers respectively)\(^4\). Many studies have used a level of block to pinprick at T4 to indicate adequate anesthesia for Caesarean section\(^2,4\). However, results of these investigations indicate that pinprick to T4 is unreliable in predicting the adequacy of spinal anesthesia for Cesarean section\(^3,4\). As such, experienced clinicians may use very little formal testing, relying on other signs such as early onset of lower limb weakness, feelings of warmth, slight hypotension and altered sensation over the proposed site of surgery as a means of block assessment.
Several investigators indicate that the loss of touch sensation is the best predictor of painless surgery, as compared to the loss of cold and pinprick. This may be a reasonable alternative to the use of pinprick or cold despite the more subtle and subjective nature of such a test. Moreover, the associated noxious stimulus and potential for introducing infection involved with pinprick puts the touch modality at a clear advantage. Because of these differences, an apparently “adequate” spinal placement may not actually provide surgical anesthesia because the block has been tested using a stimulus of significantly different modality or intensity than the planned surgery.

Pain during surgery can occur despite altered sensation over the surgical site for several reasons. A simple, single stimulus (e.g. pinprick, cold) may be blocked, but only accurately tests responses to that stimulus in the local area. Surgery involves multiple forms of afferent stimulation and spinal cord mechanisms may result in repeated stimuli (temporal summation), or stimuli from adjacent regions (spatial summation), evoking pain and leading to a “failed block” and poor image for the anesthesiologist.

In this case, the patient’s prior abdominoplasty resulted in a downward shift of dermatomes of the anterior abdomen. Thus, the use of pinprick to assess the anesthetic level gave the false perception of an inadequate block. Having understood the consequences of an abdominoplasty and its effect on the dermatomal anatomy, a pinprick test on the posterolateral aspect of the patient’s abdomen was performed. Our suspicions were confirmed and the patient displayed a block at the T5 level. Despite correct administration of the test, as in this case, one could have easily been mislead to think that the spinal block was inadequate. This underscores the importance of a fundamental knowledge of anatomy applied to the anesthetic principles of a neuraxial block. While visceral blockade was sufficient for the planned surgery, skin sensation remained intact.

Conclusion

Abdominoplasty is common after weight loss surgery. These procedures are performed as anterior and/or circumferential abdominoplasty or torsoplasty, a surgery that involves removal of excess skin of the trunk in addition to abdominal skin, making accurate level assessment of subarachnoid block virtually impossible because of dermatome changes. Often patients do not report cosmetic procedures when recounting a surgical history and plastic repairs may make incisions difficult to identify. A high index of suspicion should be maintained in patients with retained anterior skin sensation after uneventful placement of a subarachnoid block, especially if there is a history of weight loss surgery with considerable positive results. Until additional methods of assessing spinal block levels are developed that are practical, accurate and easily reproducible, maximizing the accuracy of the current methods can be achieved by understanding their differences and limitations. The use of the light touch modality may be more appropriate in the clinical setting given the poorer predictive power of cold and sharp pinprick tests.

While we report on a case of Cesarean section, males also frequently undergo weight loss surgery with plastic repair at a later date. They may also present for abdominal or urologic surgery that is managed by neuraxial block. Again, a level of suspicion should be maintained.
References


ANESTHETIC MANAGEMENT OF CHILDREN WITH RUBINSTEIN-TAYBI SYNDROME

- Case Reports -

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Abstract

A limited number of cases of anesthetic management of Rubinstein-Taybi Syndrome (RTS) have been reported since this syndrome was first diagnosed in 1963. After some well-publicized complications following anesthesia for patients with RTS, there has been great interest in avoiding all precipitant factors and careful monitoring during intraoperative and postoperative periods.

This case series examines the cases of three pediatric patients with RTS who presented to the Children’s Hospital of Michigan for different surgeries. We aim in this study to share information about this rare syndrome and to emphasize how this case series allowed us to improve our anesthetic management. In each case, we adjusted our techniques using information from preceding cases to avoid complications in the following encounter.

Introduction

RTS is a rare congenital anomaly that affects many organ systems of the body with a frequency of approximately 1 in 100,000 newborns\(^1\). The findings associated with this syndrome include growth retardation, delayed bone age, mental retardation, abnormally broad thumbs and great toes, breathing and swallowing difficulties. Most affected children experience delays in attaining developmental milestones and delays in the acquisition of skills requiring coordination of muscular and mental activity (psychomotor retardation). In addition, many individuals with RTS may have malformations of the heart, kidneys, urogenital system, and/or skeletal system. The abnormalities of the head and face include widely spaced eyes (hypertelorism), a broad nasal bridge, an abnormally large or "beak-shaped" nose, and an unusually small, hypoplastic lower jaw (micrognathia) with small mouth opening. The classical facial appearance is well-established, striking and easy to recognize.

Due to their craniofacial abnormalities, delayed development and gastroesophageal reflux disease (GERD), these patients are prone to difficult intubation and airway compromise\(^2\). These features may complicate not just the intraoperative anesthetic management, but also cause problems in the immediate and late postoperative period.

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Case 1 A

The first patient was diagnosed with RTS at 2 weeks of age, after unremarkable term delivery. He had typical broad thumbs, broad first toes, large forehead, low set ears, anti-mongoloid slant of the palpebral fissures, bilateral undescended testes, bilateral renal calculi, renal tubular acidosis, cholelithiasis, hypotonia, mild GERD, and severe developmental delay. His echocardiogram showed a small patent foramen ovale, mild mitral valve regurgitation with preserved ventricular function. There were no features suggestive of abnormal airway.

At 9 months of age and a weight of 4.5 kg, he presented for MRI of the spine under general anesthesia. No difficulty in intubation was encountered with a Miller 0 laryngoscope blade and a 4.0 uncuffed endotracheal tube (ETT) and the patient had an uneventful intra-procedural course. There was no mention in the anesthesia record of any audible leak heard around the ETT. The anesthesia consisted of isoflurane, 1 mcg/kg of fentanyl and 0.5 mg of pancuronium. After a short stay in the postoperative care unit, he was discharged home. The following day, he developed respiratory distress necessitating a visit to the emergency department where he was found to have copious secretions. Chest x-ray showed no evidence of pneumonia. After thorough suctioning of the airway and several hours of observation, the patient improved and was sent home.

Case 1 B

The above patient presented a month later at 10 months of age and a weight of 4.8 kg for laminectomy and release of tethered cord. The patient was induced with 50% N\textsubscript{2}O/O\textsubscript{2} and 8% sevoflurane using a face mask. An IV access was started and propofol 2 mg/kg, fentanyl 2 mcg/kg and vecuronium 0.1 mg/kg were given. On this occasion a smaller sized tube was chosen to minimize the likelihood of airway trauma, edema, or tracheomalacia. Gentle mask ventilation was followed by an easy intubation with a 3.5 uncuffed ETT using a Miller 0 laryngoscope blade and secured at 11 cm after confirmation of bilateral air entry. No audible leak was noted with the smaller tube size, which suggested that the size 4 ETT used in the previous anesthetic in this patient one month was inappropriately large. The patient was turned prone and anesthesia was maintained with isoflurane in 50% O\textsubscript{2}/air and propofol infusion at 150 mcg/kg/min. No further doses of neuromuscular blockers were given.

The surgery lasted approximately 4.5 hours. The trachea was extubated after the patient was fully awake and after thorough suctioning of his airway. His postoperative course was uneventful and was discharged home on postoperative day 3.

Case 2

A 10 year old boy presented for dental restoration because of advanced dental caries. Our patient showed many of the typical craniofacial features of RTS and significant developmental delay. Examination showed a boy of short stature weighing 30 kg. He had a prominent broad nasal bridge, arched thick eyebrows and a prominent beaked nose. No obvious anomaly of the maxilla or upper jaw was noted. However, the patient had a small mouth and adequate but limited mouth opening which may reflect poor development and malpositioning of the mandible or lower jaw that is often seen with RTS.
Before induction, we made sure that equipment necessary to manage difficult airway were immediately available. We induced anesthesia with 70% N₂O/O₂ mixture in sevoflurane 8% via face mask and intubated using a smaller tube than normal based on our experience in the previous case. His heart rate was 145 bpm, SpO₂ 97% and BP 110/60 mmHg. After IV access was obtained 1 mcg/kg of fentanyl and 0.05 mg/kg of vecuronium were injected.

Because choanal atresia and a deviated nasal septum has been described in RTS, the nasal mucosa was well prepared with oxymetazolone (Afrin). A red rubber suctioning tube was used as a guide for the 5.5mm nasal RAE tube to assess the patency of the naris and to avoid trauma. The right naris was found to be obstructed however; the tube was easily advanced in the left naris. At laryngoscopy, a very high arched palate was confirmed and the cords were partially seen (Cormack Grade II). Intubation was uneventful.

Anesthesia was maintained with isoflurane 1.5% in 50% oxygen/air. Interestingly, there were three documented episodes of self-limiting oxygen desaturations to 90% without any provocation. The surgery lasted 2½ hours. To avoid the risk of arrhythmia, anticholinesterase was not given, with no evidence of residual muscle relaxant effect. Good airway and gastric suctioning was performed and the patient was extubated ten minutes later when fully awake without any complications.

Case 3

A 4 year old boy presented for dental restoration because of advanced dental caries. He had many craniofacial features of RTS and global developmental delay. Again, equipment necessary for difficult airway were immediately available. After uneventful mask induction with 70% N₂O/O₂ mixture and sevoflurane, the nasal mucosa was prepared with oxymetazolone (Afrin). Despite this preparation there was bleeding in the posterior pharynx that obscured the view of the vocal cords and led to failed intubation on first attempt. After repeated suctioning, intubation was successful at the third attempt. Anesthesia was maintained with isoflurane 1.5% in 50% oxygen/air. Opioids were kept minimal with a total dose of 2 mcg/kg fentanyl IV. Good airway and gastric suctioning was performed and the patient was extubated when fully awake without any complications.

Discussion

In this case series we collected information about RTS and our anesthesia techniques for four anesthetics and the following are the lessons learned:

1. Copious secretions causing airway compromise has been reported in literature and was seen in our case#1A. We resorted to careful oropharyngeal and endotracheal suctioning prior extubation to avoid this complication in the subsequent three cases. We also confirmed accurate placement to avoid endobrochial intubation during changes in patient positioning and subsequent atelectasis.

2. Intraoperative self-limiting desaturations to 90% were seen in case #2 without any provocation and these have been reported by Critchley et al. Respiratory infections and complications are major causes of morbidity and mortality in the first years of life. Studies have shown that breathing disturbances occur in 11% of subjects with RTS.

3. Airway narrowing and tracheomalacia is always a possibility and could have been the cause of
postoperative airway compromise in case 1A. Hannekam et al have reported abnormal upper and lower airway narrowing in non-anesthetized subjects with RTS\(^6\). To avoid airway trauma and tracheomalacia, we deliberately used a relatively smaller sized endotracheal tube in our patients.

4. Cardiovascular abnormalities are not uncommon in these patients\(^5\). In case #1B, we carefully avoided bradycardia and increased afterload in order to prevent worsening of mitral regurgitation fraction and subsequent reduction of the cardiac output. Our patient also had a patent foramen ovale, so we were very vigilant in avoiding air bubbles in the intravenous line to prevent paradoxical emboli. These cardiac abnormalities also predispose to arrhythmias with the use of arrhythmogenic drugs like succinylcholine, atropine and neostigmine\(^3\). We therefore avoided the use of the aforementioned drugs and our patients did not have any arrhythmia at any time during the hospital stay.

5. Epistaxis complicating airway management occurred in case #3. Though this cannot be labeled as difficult intubation, yet in these patients a difficult airway should always be anticipated and an emergency airway cart including a fibreoptic bronchoscope should be available, despite history of easy intubations during prior anesthetics in the same patient.

6. Delayed recovery after general anesthesia in these patients is also a concern and has been reported in literature\(^7\). In our case series, we did not encounter this problem, though we were well prepared for it.

**Conclusion**

Children with RTS vary widely in the range and severity of symptoms and physical findings as well as the complications developed during the perioperative period. Whatever the phenotypic presentation of patients with RTS, the physical challenges to the anesthesiologist should always be centered about three main areas: craniofacial anomalies, airway and pulmonary complications and cardiac anomalies. We strongly suggest careful planning of the anesthetic and airway management with close observation and monitoring extending well into the postoperative period.

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Dear Editor,

Proseal laryngeal mask airway (PLMA) is now standard of care in many institutions due to lower risk of aspiration and better capability of ventilation\textsuperscript{1,2}. We report a case where broken tip of silicon coating of the metal introducer of PLMA caused airway obstruction in an anesthetized patient.

A twenty-four year old male patient was scheduled for varicose vein stripping of left lower limb under general anesthesia. Pre-anesthetic evaluation was insignificant. General anesthesia was induced with propofol (2.5 mg.kg\textsuperscript{-1}) and fentanyl (2 mcg.kg\textsuperscript{-1}). After achieving adequate plane of anesthesia, a size four PLMA mounted on a standard introducer (which comes along with the PLMA) was inserted. After an initial failed attempt by a resident, LMA could be successfully inserted by the consultant anesthesiologist. Adequate placement was checked with acceptable chest rise with manual ventilation, bilateral equal breath sound on auscultation and appearance of regular end tidal capnogram on monitor. Patient was kept in spontaneous respiration and adequate depth of anesthesia was maintained with oxygen in 60% nitrous oxide and sevoflurane. Under strict asepsis, femoral, obturator and popliteal nerve blocks were performed with 0.25% bupivacaine under combined nerve stimulator and ultrasound guidance.

After about 15 minutes, patient’s breathing became noisy and stridulous. Suspecting the anesthetic plane to be inadequate, anesthesia was deepened by increasing sevoflurane concentration. But, it did not solve the problem and he became more tachypneic with low tidal volume and end tidal carbon dioxide increased to 55 mmHg. The problem continued even after repositioning the PLMA by gentle manipulation, deflating and inflating the cuff, manually assisting the ventilation. It was decided to change the PLMA under direct laryngoscopy by bougie guided technique\textsuperscript{3} as the patient desaturated from 99% to 94%. PLMA was removed without delay. While suctioning the oral cavity under direct laryngoscopy a blue colored foreign body was found in the oropharynx, which was removed by Magill’s forceps. After mask ventilation with 100% oxygen and deepening the plane of anesthesia with additional bolus of propofol, a new size four PLMA was successfully placed with the help of a bougie. Correct positioning of PLMA was confirmed as before. Rest of the procedure including the post-anesthesia recovery was uneventful. The blue colored piece was found to be the broken part of the tip of silicon coating of the metal introducer of PLMA (Fig. 1).

\textbf{Fig. 1}

\textit{Broken Proseal LMA introducer and an intact introducer for comparison}

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Partial airway obstruction with PLMA can be due to various reasons such as malposition, folding of distal part of the cuff, backfolding of epiglottis, infolding of aryepiglottic fold, cuff herniation, excessive cuff inflation, obstruction of laryngeal opening by cuff, infolding of the bowl of PLMA, faulty PLMA, presence of foreign body, laryngospasm, stridor. Although soap bubble test helps in detection of malposition, best possible way to differentiate between the causes is passing a fiberscope through PLMA which is not always practicable. Therefore, the exact cause often remains obscure and various techniques such as gentle reposition, inflation and deflation of cuff and finally removal and reinsertion of PLMA are used to achieve proper position and adequate ventilation.

Although LMA supreme, the disposable version of PLMA, is available in market, its use is not widespread enough to replace the reusable version. Breakage of the parts of LMA leading to airway problems has been reported before particularly if the LMA is used beyond its life span. But, in our case, the problem was the silicon coating of the introducer, which broke apart at the tip. Potential complications can be airway obstruction, injury, esophageal and tracheal aspiration, all of which can be fatal. Trying to reposition the PLMA in this case can push the foreign body into trachea and may pose real threat to patient’s life.

Best management is prevention of this complication. Most hospitals, including us, are very careful in tracking the number of use of reusable PLMA and limit it to a maximum of 40 times so as to prevent any
mishap\textsuperscript{10}. The protocol should be valid for the silicon coating of PLMA introducer as well. However, this may not be true for every PLMA introducer as the silicon coating may be weakened and damaged during multiple insertion attempts as it usually comes in contact with the teeth of the lower jaw. This complication can easily be prevented by being little attentive towards the integrity of not only the PLMA but also the introducer properly before and after use.
References